A CLINICO-GENETIC ANALYSIS OF AUTOSOMAL DOMINANT SPINO CEREBELLAR ATAXIAS IN THE INDIAN POPULATION

Dissertation submitted to the Dr M.G.R Medical University, Chennai, Tamil Nadu, in fulfillment of the DM - Neurology university examinations in August 2010

CERTIFICATE

This is to certify that the Dissertation titled "A Clinico Genetic Analysis of Autosomal Dominant Spinocerebellar Ataxia in an Indian population" is the bonafide work of Dr. Krishnan Balagopal S submitted in fulfillment of the DM – Neurology examination conducted by the Tamil Nadu Dr. M.G.R Medical University, Chennai, in August 2010

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ABSTRACT

TITLE- A CLINICO-GENETIC ANALYSIS OF AUTOSOMAL DOMINANT SPINO CEREBELLAR ATAXIAS IN THE INDIAN POPULATION

DEPARTMENT- NEUROLOGY

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INTRODUCTION- Spinocerebellar ataxias are neurodegenerative diseases characterised by progressive degrees of cerebellar ataxia along with ophthalmoplegia and pyramidal signs with peripheral neuropathy. There are few studies looking at the prevalence of various subtypes in Indian populations. This study aims to look at the clinical features and do genetic testing for a population of familial cases of spinoocerebellar ataxia near Adigambarai village ,Vellore and to ascertain clinic genetic co relations and also comparison with a hospital group of Spinocerebellar ataxia.

OBJECTIVES-Neurological testing and pedigree analysis of an endemic area with familial cases of spinocerebellar ataxia and a hospital population of spinocerebellar ataxia and to ascertain clinico genetic correlates and also comparison of the hospital and familial groups with respect to age of onset ,patterns of inheritance and clinical features.

METHODS- The familial group of patients near Adigambarai village, Vellore would be subjected to a comprehensive neurological examination and also detailed pedigree analysis. Genetic testing would be done for both SCA-1 and also SCA-2 with extraction of DNA from buccal washings. Imaging and also nerve conductions and evoked potentials would be done. Hospital cases with positive family history presenting to CMC hospital, Vellore would also be looked at. The clinico genetic co relations and also comparison of the hospital and the familial cases would be looked at.

RESULTS-95 patients were recruited into the study of which 85 were from the familial group and 10 were from the hospital group.18 % of the familial group-15 cases were clinically symptomatic while 70 of them were asymptomatic. The sporadic group were all symptomatic.Gait ataxia was the commonest symptom followed by limb inco ordination ,slurred speech, and bulbar dysfunction. Detailed analysis of the patterns of inheritance was done .The phenomenon of anticipation was seen along with the observation that paternally inherited cases had an earlier age of onset. Genetic testing revealed that all of the hospital cases as well as the 15 symptomatic cases were positive for SCA-1.Out of the asymptomatic cases.21 of them were genetic testing positive. Some of them had subtle clinical signs and need to be followed up for age of onset and clinical manifestations.

There were intra familial differences among the familial group as regards the age of onset and the clinical features. Comparison of the hospital and familial groups also revealed differences in the age of onset, severity of disease and also the clinical features. Imaging showed predominantly features of an OPCA pattern in the majority.MRS done showed features of reduced NAA and Choline in the pons and cerebellum. Abnormalities were also noted in the nerve conductions and evoked potentials.

CONCLUSION: There were phenotypic heterogeneity in the familial groups as well as between the hospital and familial kindreds as regards age of onset and clinical features. Pedigree analysis showed significant earlier age of onset for paternal inheritance as well as a number of asymptomatic cases who were genetically positive. Long term follow up of these cases is needed.

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1. INTRODUCTION:

The autosomal dominant spinocerebellar ataxias (SCAs) are a complex group of neurodegenerative disorders characterized by progressive cerebellar ataxia of gait and limbs variably associated with ophthalmoplegia, pyramidal and extrapyramidal signs, dementia, pigmentary retinopathy and peripheral neuropathy

Disease onset is usually between 30 and 50 years of age, although early onset in childhood and onset in later decades after 60 years have been reported. The prognosis is variable depending on the underlying cause of the spinocerebellar ataxia subtype. Epidemiological data indicate that SCAs might be more common than that previously estimated with prevalences of up to 5–7 in 100 000 in some populations .This is similar to the prevalence of other uncommon motor neurodegenerative diseases, such as Huntington's or motor neuron diseases. Founder mutation effects appear to contribute to the variable prevalence detected in specific SCA subtypes

At least 28 distinct loci are responsible for
rare Mendelian forms of SCA . Interestingly, a few
SCA subtypes, including SCAs 1, 2, 3, 6, 7, 17 and dentatorubral
pallidoluysian atrophy (DRPLA), are caused by the
expansion of a CAG (DNA sequence coding for glutamine)
repeat sequence located within the coding region of specific
genes, leading to an abnormally long polyglutamine (polyQ)
tract in the encoded proteins named ataxins 1, 2 and 3, alpha
1A-voltage-dependent calcium channel, ataxin 7, TATA box
binding protein (TBP) and atrophin 1, respectively. These
SCAs show, as common features, the progressive neurodegeneration
of neuronal subsets in distinct brain areas
and the formation of polyQ-containing protein aggregates
forming characteristic nuclear or cytoplasmic inclusions
. The age at onset and severity of
disease symptoms inversely correlate with the length of the
glutamine repeat. A second group of SCAs, including SCAs 8,
10 and 12, are caused by a repeat expansion located outside of
the coding region of the disease genes leading to dysregulation
of gene expression

Numbers for the prevalence and types of SCA syndromes in Indian

populations are scattered.India is an ethnically and religiously diverse population.The ethnic diversity may have a bearing on the prevalence of the various SCA subtypes.The most common SCA type reported in India is SCA 2.The other SCA types reported from India are SCA1, SCA12 and SCA3.

In a community that lives in certain villages around Adigamparai,Vellore district, a high prevalence of SCA has been observed over decades.The villages include Rajapalayam,Kottamedu and also Santhapalli near Vellore.This study aims to carry out genetic and neurological tests for SCA1 and SCA2 among this cohort.There is a need to do genetic testing in SCAs and obtain genotypic-phenotypic correlations in different ethnic populations.This would allow for precise classification of the SCA subtype which in turn would help in genetic counselling,predictive testing ,study of natural history and progression of the various subtypes of SCA.This study aims to be a precursor for establishing how changes at the molecular and cellular level lead to neurodegeneration and also help in the development of potential therapeutic targets.

2. AIMS AND OBJECTIVES

1. Neurological testing and pedigree analysis of SCA patients in the village of Adigambarai for determining SCA subtypes based on phenotype and identifications of SCA subtypes in hospital cases with positive family history referred to CMC Vellore.

2. To characterise the phenotype in detail and then ascertain the genotype as SCA 1 or SCA 2 and look for clinical co relations.

3. To compare the hospital and the familial SCA kindreds with regards to the age of onset, disease severity and clinical features.

3. REVIEW OF LITERATURE

The term spinocerebellar ataxias (SCA) has been used to denote recessive and sporadic disorders, and neuropathologists have defined SCA as cerebellar ataxias with involvement of the spinal cord.

Prevalence and incidence

Epidemiological data about the prevalence of SCA are restricted to a few studies of isolated geographical regions, and most do not reflect the real occurrence of the disease. In general a prevalence of about three cases per 100 000 people is assumed, but this may be an underestimate.[1,2] As SCA are highly heterogeneous, the prevalence of specific subtypes varies between different ethnic and continental populations.[3] Most recent data suggest that SCA3 is the commonest subtype worldwide; SCA1, SCA2, SCA6, SCA7, and SCA8 have a prevalence of over 2%, and the remaining diseases are thought to be rare (prevalence <1%).This figure has to be adjusted, as some “rare” genotypes such as SCA14 or SCA17 have not been included in previous population studies.[4] Also, for gene loci that have been linked to a chromosomal region but for which the underlying gene defect has not been identified

epidemiological data are missing because of the lack of large families suitable for linkage analysis. The proportion of undiagnosed patients with SCA in large surveys may vary between a third (the USA, the Netherlands, Japan) and a fifth (Brazil). Founder effects—genetic bias owing to the genotypes of the founding individuals in a population—contribute to these regional differences.

Genetic causes of SCA

24 autosomal dominant ataxias—SCA 1–8, 10–19, 21–23, and 25, dentatorubral-pallidoluysian atrophy (DRPLA), and ataxia caused by mutations in the gene that encodes fibroblast growth factor 14 (*FGF14*)—have been identified. In 12 of these disorders the genes involved and the underlying mutations are known.[5] Six SCA subtypes (SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17) and DRPLA are caused by CAG trinucleotide repeat expansions in the respective genes. These expansions encode polyglutamine repeats, as in Huntington's disease (HD); and these diseases are also known as polyglutamine expansion disorders.

Besides CAG repeats in the coding regions, a CAG

repeat expansion of more than 66 repeats has been found in the 5_ region of the *PPP2R2B* gene11 in families with SCA12 .Although the exact position of the expanded CAG repeat in the region of the *PPP2R2B* gene is still a matter of debate (5_ untranslated region, promoter region, or part of exon 1) it does not encode a polyglutamine tract.

In SCA10, the functional implication of a pentanucleotide-repeat expansion in intron 9 of a gene of unknown function has not been defined in detail. The disease causing expansion is 800–4000 ATTCT repeats, which makes PCR based approaches for DNA testing difficult.

For SCA8, whether an unstable and expanded CTG repeat is indeed causal or only associated with the disease is still debated.

Two autosomal dominant ataxias are caused by point mutations: mutations in *FGF14* segregate with the SCA phenotype, and families with SCA14 have mutations in the gene encoding protein kinase C _, *PKC_*.[6]

Repeat instability and genetic testing

For SCA subtypes caused by repeat expansions, the age at onset is inversely correlated with repeat length .[7,8]

Thus small expansions are found in patients with late onset of symptoms. Small expansions that are sometimes close to the normal repeat range (SCA2, SCA6), may have reduced penetrance and may thus appear as sporadic disease without a family history.

The expanded, longer than normal, repeats are unstable and tend to expand further. This leads to earlier age at onset and a more severe phenotype in successive generations—a phenomenon known as anticipation. Most cases of childhood onset are caused by extreme expansions between generations. For larger repeat expansions as in SCA3, somatic instability might occur making a genotype–phenotype correlation even more problematic.[10] Thus precise prediction for the age at onset cannot be given in presymptomatic testing. Special caution has to be taken in prenatal diagnosis owing to the instability of the repeat during transmission in particular if the father is affected. Extreme expansions in sperm have been observed for SCA7 and SCA2 [11]

Genetic counselling is similarly difficult in individuals with alleles of intermediate repeat length. These alleles are

unstable during meiosis and may expand into the pathological range. These repeats have expanded during evolution. Thus, fish, mice, non-human apes, and human beings have increasing repeat length in the affected genes, which is one reason why naturally occurring mouse models for repeat expansion disorders do not exist.

Pathogenesis

CAG repeat expansions

For most types of SCA caused by CAG repeat expansion in the coding region of a gene the functions of the affected proteins are still unknown; the exceptions are SCA6, which encodes the _1A-subunit of a P/Q-type calcium channel, and SCA17, which encodes TATA-box binding protein (TBP).[12,13] Except for the polyglutamine repeats, the affected proteins have no common sequences or domains. Therefore it is assumed that the pathogenesis is directly linked to the expanded polyglutamine stretch.[14] Indeed, transgenic mice expressing expanded polyglutamines in a foreign protein (hypoxanthine phosphoribosyl transferase) develop a neurological phenotype and neuropathological features

similar to polyglutamine diseases.[15]

Much has been learned about these disorders from the analysis of Huntington's disease, in which polyglutamine repeats of more than 38 residues cause disease. In 1994, Perutz and colleagues[15] suggested that expanded polyglutamines can form _-sheet structures and can link proteins via "polar zippers". Huntingtin fragments containing expanded polyglutamine repeats can form insoluble aggregates in vitro whereas samples with polyglutamines at normal length remained soluble. Protein aggregates are a hallmark of all polyglutamine diseases. With a few exceptions protein aggregates were described in neurons of affected brain regions of people with SCA27,[16-18] and the term neuronal intranuclear inclusion bodies became widely used in association with these disorders. In SCA2, however, aggregates are found in the nucleus and the cytoplasm, whereas in SCA6 inclusions were found only in the cytoplasm.

The localisation of the polyglutamine protein within cells seems to be important: whereas ataxins normally show cytoplasmic localisation, nuclear transport might be a key

issue for the induction of neurodegeneration .[19]
Furthermore, axonal transport defects might contribute to disease progression.
Analysis of the composition of the nuclear inclusions uncovered that they contain only the part of the protein that contains the polyglutamine repeat. In Huntington's disease, the protein seems to be cleaved by caspases before being transported into the nucleus and before aggregates can be formed . Caspases, however, do not seem to have a major role in the modification of ataxins, which indicates that there are differences in the pathogenesis of different polyglutamine diseases

Recent research showed that not only the polyglutamine stretch but also the remaining protein context plays an important part in the pathogenesis: in SCA1 for example, 14-3-3 proteins bind to ataxin 1 after phosphorylation of a specific serine residue (S776) by Akt kinase which stabilises ataxin 1 and leads to accumulation and aggregation.[20]
Another important mechanism in the formation of nuclear inclusions is related to the ubiquitin–proteasome pathway. Ubiquitin is used to tag proteins for disposal by

proteasomes. Ubiquitin, as well as several proteasomal subunits, were found in neuronal inclusions.[21] The distribution of these subunits in nuclear inclusions, however, points to a perturbation of proteasomal function in patients.Several approaches highlight the importance of ubiquitin as a marker for polyglutamine-disease pathogenesis. After interruption of the ubiquitin machinery fewer inclusions are observed but neurodegeneration proceeds. The mutant proteins might be far more toxic if they are not sequestered into inclusions. The formation of inclusions could, therefore, be a protective mechanism against the toxicity of expanded polyglutamine proteins.

Region-specific cell death in SCA

Cell-type-specific expression patterns of mutated genes do not explain region-specific cell death in different SCA subtypes. Interacting proteins might contribute to the selectivity of the neurodegenerative process. Only for two SCA subforms, SCA1 and SCA7, have matching candidates for the region specific to neuronal cell death been identified: the Leucine-rich acidic nuclear protein, LANP, interacting

with ataxin 1 might explain neurodegeneration of Purkinje cells observed in patients with SCA1 and the cone–rod homeobox protein, CRX, which interacts with ataxin 7, might contribute to retinal degeneration in SCA7.

Other identified interaction partners cannot explain the regional distribution but do add to our understanding of pathogenesis. For example, binding of expanded polyglutamine stretches to the polyglutamine binding protein PQBP 1 can affect transcription. Additionally, ataxin 3 interacts with cAMP response element-binding protein (CREB)-binding protein, a coactivator of many transcription factors.Polyglutamine stretches can also interact with TAFII130, another coactivator of CREBdependent transcription activation. Moreover, the CREB binding protein[22] and the TATA binding protein are recruited into intranuclear inclusion bodies highlighting their relevance to the pathogenesis of spinocerebellar ataxias. Therefore, differences in expression seem to be connected in particular with CREB and TATA dependent transcription.

genes, disturbed protein degradation,
the aggregation of proteins, disturbed
transcription, altered vesicle transport,
or a combination of these mechanisms
trigger the death of neurons is
unknown.

Clinical features of ataxias

SCA have a wide range of neurological symptoms including
ataxia of gait, stance, and limbs, cerebellar dysarthria,
oculomotor disturbances of cerebellar and supranuclear
genesis, retinopathy, optic atrophy, spasticity, extrapyramidal
movement disorders, peripheral neuropathy,
sphincter disturbances, cognitive impairment, and epilepsy.
The clinical diagnosis of specific subtypes is complicated by
the huge overlap of the phenotype between genetic subtypes
and substantial variability of clinical features within a
distinct genetic subtype. This explains why nearly no clinical
sign is specific for a genetic subtype .[23,24,25]

SPINOCEREBELLAR ATAXIA TYPE 1

Spinocerebellar ataxia 1 (SCAl) is an autosomal dominant disorder that is

clinically characterized by progressive limb and gait ataxia, dysarthria, and variable degrees of pyramidal tracts signs, brain stem symptoms, and peripheral neuropathy.

The neuropathological findings in SCAl include neuronal loss in the cerebellar cortex and brain stem, as well as degeneration of the spinocerebellar tracts. The SCAl locus was the first ataxia disease locus that has been defined. Based on linkage to HLA loci, the SCAl gene was mapped to chromosome 6p [26]. In 1993, Orr et al. isolated the SCAl gene and showed that the mutation is an unstable CAG trinucleotide repeat expansion within a translated region of the gene. As in other CAG repeat disorders, the pathogenetic mechanism is not the loss of physiological function of ataxin-1, but rather the gain of a new deleterious function

Recent epidemiological studies yielded prevalence rates of dominant ataxias ranging from 0.9 :1 00,000 to 1.3: 1 00,000 [27-28] The proportion of SCAl among all mutations causing dominant ataxia varies considerably among different populations.

NEUROPATHOLOGY

There is only a limited number of necropsy studies in SCAl .The findings typically involve degenerative changes, with neuonal cell loss and gliosis in the cerebellar cortex, pontine nuclei, and inferior olives, compatible with a neuropathological diagnosis of olivopontocerebellar atrophy. Often, there is

additional cell loss in the caudal cranial nerve nuclei, Degeneration within the basal ganglia, thalamus, and cerebral cortex are less frequent. In the spinal cord, axonal loss and pallor of myelin is observed in the dorsal column pathways, spinocerebellar tracts, and less frequently, in the pyramidal tracts [29]

Cerebellar Purkinje cells are usually most severely affected by using Golgi techniques and immunohistochemical methods, dendritic simplification with loss of spines has been described[30]

In general, the distribution and severity of neuropathological changes in SCAl is quite variable, even within one family

Nuclear inclusions are ultrastructural hallmarks of most CAG-repeat disorders. Their significance for the pathogenesis of SCAl is discussed in the foregoing .[31] Autopsy examination of one SCAl patient revealed additional neuropathological alterations, reminiscent of multiple system atrophy with demonstration of oligodendroglial cytoplasmatic inclusions [32]. However, the density of these inclusions in the SCAl brain was much lower than in multiple system atrophy.

V. CLINICAL FEATURES

A. Disease Onset, Progression, and Survival

Disease onset in SCAl varies between adolescence and late adulthood. On average,the disease starts at about the age of 35 years [33].T he earliest reported disease onset occurred in a patient from a Iakut kindred in eastern Siberia who noticed onset of ataxia at the age of 15 years . Almost all SCAl

patients develop first symptoms before the age of 55 years. As in other CAG repeat disorders, there is an inverse correlation between CAG repeat length and age of onset. Anticipation has been observed in many SCAl families.

SCAl always takes a progressive course, and may lead to severe disability and premature death. A recent epidemiological study reported a median latency to become wheelchair-bound after disease onset of l4 years. Median survival after onset of symptoms was 21 years, and median age at death 56 years . This result corresponds well with data from a series of 14 autopsied SCAl cases in which mean age at death was 54 years .

B. Clinical Presentation

All SCAl patients suffer from a progressive cerebellar syndrome, with ataxia of gait and stance, ataxia of limb movements, dysarthria, and cerebellar oculomotor abnormalities [34-36]. The oculomotor abnormalities include gaze-evoked nystagmus, saccade hypermetria, broken-up smooth pursuit, reduced optokinetic nystagmus, and impaired suppression of vestibulo-ocular reflex by fixation [37,38.]

In most patients, there are additional noncerebellar symptoms. About half of the patients have supranuclear gaze palsy or saccade slowing; or both. Pyramidal tract signs with spasticity, extensor plantar responses, and hyperreflexia are found in more than 50% of patients with SCAl. In contrast, depressed or absent tendon reflexes and amyotrophy are only rarely

encountered.

Usually, there are no severe sensory disturbances. However, decreased vibration sense is found in up to 80% of the SCAl patients. Dysphagia is a frequent complaint of SCAl patients,and it is a particular clinical problem in late disease stages.

Disturbances of sphincter control, mainly bladder dysfunction, occur less frequently, and are encountered in about 20% of the patients. Basal ganglia symptoms, with parkinsonism or dystonia have been observed only in single patients .Mental disturbances are encountered in fewer than 10% of SCAl patients.

In advanced disease stages,amnestic and cognitive deficits may occur. Some patients develop clinically manifest dementia [39]. In addition, affective disturbances, personality changes, and behavioural disorders have been observed.

These disturbances include irritability, inadaequate euphoria, aggressiveness, and nocturnal crying [39]. These clinical observations are in good accord with the results of a study in 11 SCAl patients that used standardized neuropsychological tests. This study reported deficits of verbal and nonverbal intelligence, memory dysfunction, and disturbances of executive functions.T he degree of these deficits was correlated with the severity of ataxia [40].

C. Correlation of Clinical Presentation with Disease

Duration and Repeat Length

Clinical presentation of SCAl patients and severity of symptoms partly depends on disease duration and on the length of the CAG repeat. Although ataxia and pyramidal tract signs are usually present in early stages of the disease, the frequency of dysphagia, amyotrophy, hyporeflexia, sensory signs, and supranuclear gaze palsy increases with progression of the disease . A recent study from a large Siberian SCAl kindred suggested that the severity of associated symptoms, such as dysphagia, skeletal muscle atrophy, and tongue atrophy, increases with CAG repeatlength .

VI. ANCILLARY TESTS

A. Nerve Conduction

Nerve conduction studies in SCAl patients suggest presence of mild, predominantly sensory neuropathy with features of both axonal loss and demyelination[41]. Motor and sensory nerve conduction velocities are in the lower-normal range. However, conduction velocities tend to be lower than in other SCA mutations,and distal latencies may be mildly prolonged . In a study of nine patients with SCAl, amplitudes of compound muscle action potentials were reduced in only one. In contrast, more than half of the patients had low antidromic sensory nerve action potentials of the sural nerve. Needle electromyography discloses chronic neurogenic changes, but usually no pathological spontaneous activity .

B. Evoked Potentials

Motor-evoked potentials by transcranial magnetic stimulation, are almost always abnormal in SCAl. The abnormalities include prolonged central motor conduction time, reduced amplitudes, and raised thresholds. Visual-evoked potentials have been studied by two groups, yielding conflicting results. Schols et al. found delayed P100 responses in only one of ten SCAl patients ,whereas Abele et al reported a frequency of abnormal visual-evoked potentialsof almost 80%. Somatosensory-evoked potentials and brain stem auditory evoked potentials are abnormal in more than half of SCAl patients.

C. Magnetic Resonance Imaging

Tl-weighted magnetic resonance images (MRI) reveal global atrophy of brain structures in the posterior fossa, suggestive of olivopontocerebellar atrophy [42]

In addition, there is often visible atrophy of the cervical spinal cord . Quantitative studies, using planimetric and volumetric evaluation of MRI scans show that cerebellum, brain stem,and cervical spinal cord are, on average, shrunken to 70-80% of their normal size. These studies did not provide evidence for additional atrophy of basal ganglia nuclei . The question of whether there is also atrophy of the cerebral cortex has not yet been addressed. There are no obvious signal abnormalities on T2 weighted images; however, this question has not been studied systematically.

Magnetic resonance spectroscopy in SCA -1

Various studies have shown the utility of magnetic resonance spectroscopy in the diagnosis of SCA-1.
It has been found that the NAA:Creat ratios in the pons and the cerebellum were reduced as compared to normal subjects.This has been found to be an early and more sensitive change than the degree of cerebellar and brainstem atrophy seen in SCA-1.This is thought to represent a loss of neuronal viability in the brainstem and cerebellum.Also, there was a degree of correlation between the severity of ataxia and the the MRS findings in SCA1 and not in SCA 2.This may be due to the later onset and faster progression seen in SCA 1 as compared to SCA 2 .

D. Positron Emission Tomography

A positron emission tomography (PET) study in three SCAl patients, using fluorodeoxyglucose,revealed hypometabolism not only in the cerebellum and brainstem, but also in the cerebral cortex, basal ganglia, and thalamus .
Because neuropathological and MRI studies do not indicate severe degeneration in these latter brain structures, hypometabolism in the cerebral cortex, basal ganglia, and thalamus is most probably due to remote effects of cerebellar and brain stem degeneration.

Vil. MANAGEMENT

There is still no specific treatment for SCA1. Several studies suggest moderate symptomatic benefit of 5-hydroxytryptophan, amantadine, and buspirone in ataxic patients, whereas other studies were unable to confirm these findings [43,44.] All studies have been performed in heterogeneous group of ataxic patients. In addition, most of the studies were only poorly controlled. There is no study that specifically addresses the question whether or not one of these compounds is particularly beneficial for SCAl patients. Spasticity in SCAl usually does not require medical treatment.

Physical and speech therapy is recommended, although there are no studies providing convincing evidence that these therapies are effective in patients with progressive ataxia. Many SCAl patients are dependent on canes or wheelchairs within years after disease onset. Patients with severe dysphagia should be be fed by gastric tubing to avoid undernourishment and aspiration[45]

STUDIES

Ranum et al (1994)[46] studied the frequency and variability of the SCAI repeat expansion in 87 kindreds with diverse ethnic backgrounds and dominantly inherited ataxia. For 113 patients from the families with repeat expansion, inverse correlations between CAG repeat size and both age at onset and disease duration were observed.

Repeat size accounted for 66% of the variation in age at onset in these patients. After correction for repeat size, interfamilial differences in age at onset remained significant, suggesting that additional genetic factors affect the expression of the SCA1 gene product.they also proposed certain clinical features observed.

Observed in every molecularly proved SCAl patient:

Gait and limb ataxia

Dysarthria

Dysfunction of cranial nerves IX, X, and XII

Observed in every molecularly proved SCA family but not in every SCA1 patient:

Oculomotor deficits

Motor weakness and amyotrophy

Proprioceptive sensory deficits

Pyramidal tract deficits

Dystonic posturing and adventitious movements

The typical clinical findings in the genetically proved SCA1 kindreds were gait and limb ataxia, dysarthria, pyramidal tract signs (spasticity, hyperreflexia, and extensor plantar responses), and variable degrees of oculomotor findings, which include one or more of the following: nystagmus,

slow saccades, and ophthalmoparesis. In the later stages of the disease course, bulbar findings consistent with dysfunction of cranial nerves IX, X, and XII became evident. Also, dystonic posturing and involuntary movements including choreoathetosis became apparent in the later stages of the disease. Motor weakness, amyotrophy, and mild sensory deficits manifested as proprioceptive loss were also detected.

Maschke at al 2000 [47] study to identify patterns of clinical features that were likely to distinguish between SCA types and to test the specificity and sensitivity of these signs and symptoms using a Bayesian classifier. In total, 127 patients from 50 families with SCA types 1 to 8 were examined using a worksheet with a panel of 33 symptoms and signs. By computing the probabilities of each trait for each SCA type, we rated the predictive value of each feature for each form of ataxia and then combined the probabilities for the entire panel of traits to construct a Bayesian classifier. Results of this analysis were summarized in a simpler, more operator-based algorithm. Patients with SCA5, SCA6, and SCA8 demonstrated a predominant cerebellar syndrome, whereas patients with SCA1, SCA2, SCA3, SCA4, and SCA7 frequently had clinical features indicating an extracerebellar

involvement. The Bayesian classifier predicted the SCA type in 78% of patients with sensitivities between 60 and 100% and specificities between 94 and 98.2%. The highest sensitivity to correctly predict the true SCA type was found for SCA5, SCA7, and SCA8. Sensitivities and specificities found in the present study validate the use of algorithms to help to prioritize specific SCA gene testing, which will help to reduce costs for gene testing

Summary of clinical features most typical for distinct SCA types

Pigmentary retinopathy SCA7

Pure or predominant cerebellar ataxia SCA5, SCA6, SCA8

Signs of peripheral neuropathy(hyporeflexia) SCA2, SCA3, SCA4

Upper motor neuron signs(hyperreflexia, spasticity) SCA1, SCA3, SCA7

Ophthalmoplegia SCA1, SCA2, SCA3

Myoclonus SCA1, SCA2, SCA8

Chakraborty et al 2000[48]looked at 70 cases of degenerative ataxias in an ethnic bengali population .32 of these were autosomal dominant cerebellar ataxias.genotypic analysis revealed 4 cases of SCA 2, 3 cases of SCA 3 , 1 case of SCA 1 and 2 which could not be characterised.No clear pre ponderance of

one particular SCA type was seen.Slow saccades and peripheral neuropathy were seen in SCA 2 phenotypes while extra pyramidal features and distal amyotrophy were seen in SCA 3 phenotypes.

Rengaraj et al 2005 [49]conducted a study looking at the prevalence, clinical and molecular genetic characteristics of cerebellar ataxia in an ethnic Tamil community in India.An epidemiological study was done in 2 villages in Tamil Nadu where the prevalence of ataxia was high.all the people were screened and the prevalence of people with ataxia was calculated.Genetic analysis was done in those with ataxia and in 2 control groups.clinical and genetic results were co related.The total population screened was 378 of which cerebellar ataxia was found in 25.The mean age of onset was 39 years while the salient features were ataxix gait(100 %),dysarthria(100%),pyramidal signs(72%),slow saccades(48%) and bleeding diathesis(12%)

Genetic testing was done in 17 of the study group of which all showed the pathogenic expansion of CAG repeats above 40 in chromosome 6p characteristic of SCA 1.7 asymptomatic patients in the control group also had the CAG repeat above 40.

The prevalence of SCA 1 is high -7.2 % in this ethnic population with a large asymptomatic group waiting to manifest.The symptomatic individuals need support and counselling.

Krishna et al 2007[50] studied the occurrence of SCA 1,2 and 3 from a south

Indian referral hospital in Bangalore.Probands (N=318) who were diagnosed to have an ataxia syndrome (progressive degenerative ataxia of unknown cause) attending the clinical services of the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, were evaluated over a period of three years. Standard protocols were used for both clinical and molecular diagnosis. The findings suggested SCA1 rather than SCA2 to be the more common mutation in southern India. Large numbers of SCA3 probands were also identified. Differences in prevalence of these syndromes within India need to be explored further for founder effects,correlations with phenotype, and patterns of outcome. Family history was not apparent in almost a fifth of those tested positive, highlighting the value of testing even in the absence of family history. Molecular testing should be extended to cover the other forms of ataxia, of which a large number are now known. Combined efforts to confirm the presence of these less common forms, as well as family studies to detect novel mutations, are necessary in this context in India

Zulke et al[51]looked at CAG repeat expansions with loss of CAT interruptions in the coding region of the ataxin-1 gene which are associated with spinocerebellar ataxia type 1 (SCA1). For molecular genetic diagnosis it is necessary to define the limits of normal and pathological size ranges. In most studies, normal alleles as measured by PCR range from 6 ± 39

units with interruptions of 1 ± 3 CAT trinucleotides that are thought to be involved in the stability of the trinucleotide stretch during DNA replication. Expanded alleles have been reported to carry 39 ± 81 CAG trinucleotides without stabilising CAT interruptions. To evaluate the limits between normal and disease size ranges we analysed the repeat length and composition of the SCA1 gene in 15 individuals with alleles ranging from 36 and 41 triplets for genotype-phenotype correlation studies. We found the 39 trinucleotide-allele to be either interrupted by CAT repeats or formed by a pure CAG stretch. The clinical features of individuals carrying 39 uninterrupted CAG repeats did not differ from the SCA1 phenotype in general with dysphagia,pale discs, pyramidal signs and cerebellar tremor being more frequent as compared to other SCA genotypes.In contrast, the interrupted 39 trinucleotide-allele is not correlated with the SCA1 phenotype.

Bauer et al[52] reported on a family with spinocerebellar ataxia type 1 (SCA1), in which the age at onset and the severity of the disease did not correlate with the number of CAG repeat units. Although a marked anticipation was observed in the proband, it was not a consequence of an expansion of the CAG tract. None of the expanded alleles contained CAT interruptions. The pathologic expansion in this family was stable during the paternal but not maternal transmission, where it expanded by one trinucleotide and unexpectedly did not lead to anticipation. Our observations suggest that factors other than the length

of the CAG repeat play a considerable role in determination

of the disease course.

4. MATERIALS AND METHODS

The patients belonging to the cohort in the village of Adigambarai have a number of families ,each with multiple affected members of SCA. This is a community where inbreeding is prevalent and there have been no co ordinated family studies. Family history, pedigree charting and also analysis form an important part of study for any genetic disorder. Pedigree analysis with molecular studies will help us determine whether the triplet expansions behave differently in homozygous situations, expand from one generation to another(anticipation), and most importantly, do permutation alleles have any long term adverse effects on the individual.

In this study, we will undertake charting of family trees and pedigree analysis of familial kindreds in 3 villages-Kottamedu initially and then Rajapalayam and also Santhavalli at a later stage. Kottamedu village was chosen initially as it falls under the purview of the Department of Community Health(CHAD), CMC which takes care of the medical needs of this population. Patients and family members would be taken for study after informed consent. A detailed study proforma incorporating neurological history, pedigree chart and neurological examination results would be structured. There would be strict inclusion and exclusion criteria and a detailed neurological history and pedigree chart would be made.

The age of onset would be based on historical information from the patient and family members and the severity of the disease would be measured by the age of death minus the age of onset.

INCLUSION CRITERIA:

-all patients with progressive and non progressive ataxia

-family members at risk including first degree relatives of affected patients and children of the first degree relatives.

EXCLUSION CRITERIA:

Ataxia due to other etiology-nutritional/vitamin deficiency /vascular/infections/tumour

Ingestion of toxins/heavy metals/indigenous medicines

A comprehensive neurological examination would be done and ascertaining the involvement of domains outside the cerebellum. This would include cognition, cranial nerves, motor system, extra pyramidal and peripheral nervous system. A detailed pedigree chart would help in discerning the pattern of inheritance of the disorder. Patients at various stages of the disease, early into illness, established disease and advanced disease would be studied to look at the order of involvement of various systems and progression of disease and effect of anticipation on the disorder.

Patients at various stages of the disease would be identified and MR of the brain would be done to look for atrophy of the cerebellum, brainstem, cortical and subcortical structures. Visual evoked potentials would be done to ascertain

involvement of the optic nerves ,BAER to assess the involvement of the cochlear nerve pathways ,nerve conductions to look for involvement of peripheral nerves. SSEPs would be done to look for assessment of the dorsal column system. A lineage analysis of the existing cases of SCA in the villages would be done and patients for DNA testing would be identified. Buccal washings of patients would be sent for genomic DNA testing on the subtypes SCA1 and SCA2 which would be done at NCBS, Bangalore.

Sporadic cases of SCA referred to CMC Hospital would be assessed by the neurologist and clinical geneticist and buccal washings would be sent to NCBS for genomic testing on SCA subtypes. Comparison of the sporadic and endemic cases would also be done. Statistical analysis was done using the students t test, the Mann-Whitney test and using the SPSS software.

5. RESULTS

POPULATION STUDIED AND GROUPS:

The patients in the study were divided into 2 main groups.

Group 1 –consisted of patients from the cohorts of families from the affected Villages near Adigambarai, Vellore. This group included both patients clinically affected and also other members belonging to the respective families. Kottamedu village was chosen for the initial phase of this study as it comes under the follow up and area of the community health department of CMC Vellore.

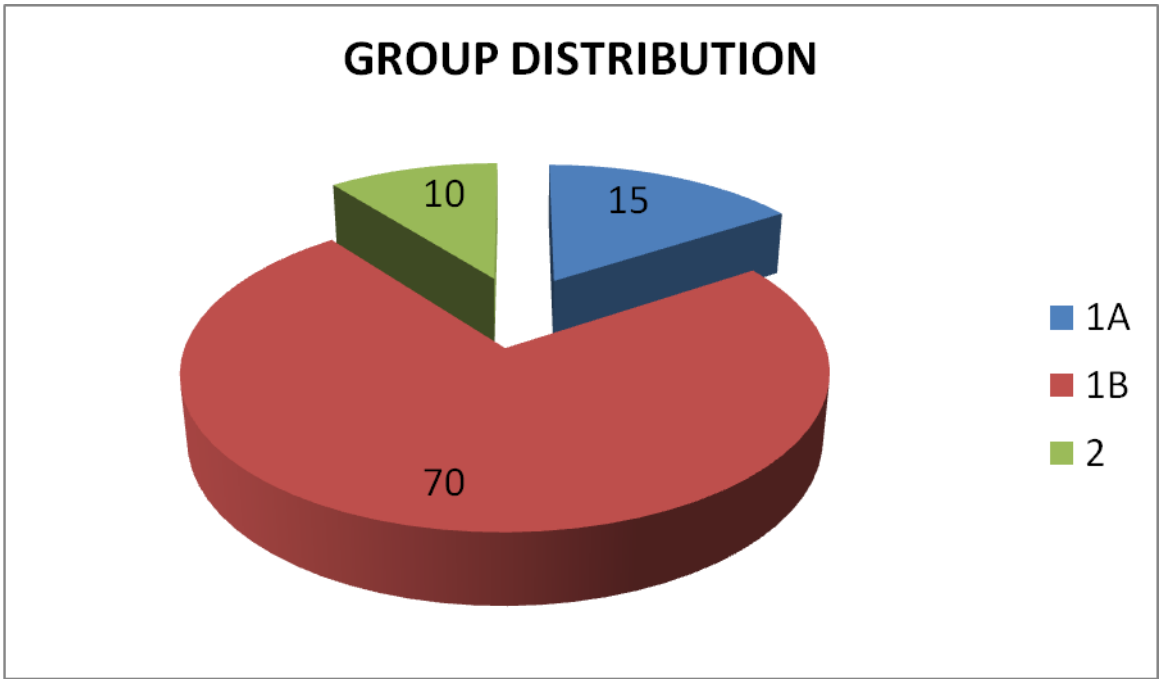
Group 2- consisted of hospital visit patients with a positive family history who were admitted in CMC Hospital during a period of 2008-10 with complaints of unsteadiness while walking and who tested positive for SCA 1 n genetic testing.

GROUP 1

There were 85 patients in this group .45 of these where male with 40 females. The patients in this group were further divided into 2 more groups. Group 1a were the patients who were clinically affected and were symptomatic for the Disease. Group b were clinically asymptomatic patients. There were 15 patients in group 1a and 70 in group 1 b.

GROUP 2

There were a total of 10 patients in this group. Of these, there were 5 males and 5 females.



GROUP CHARACTERISTICS

GROUP 1a-clinically affected

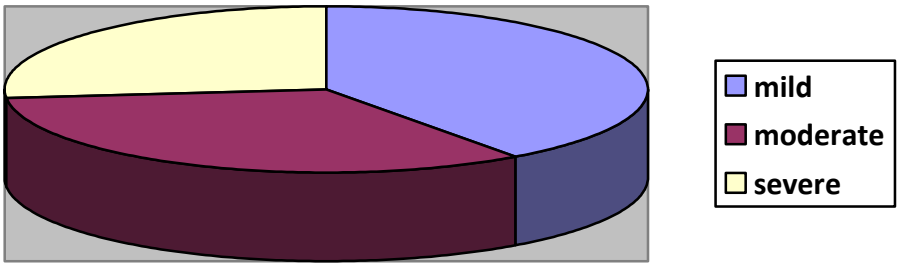
There were 15 patients in this group-9 males and 6 females.

The mean age at presentation was approximately 52 years.

The mean age of onset was around **48 years. Range-(32-68 years)**

The mean duration of symptoms was about **4 years**. The range was from 1 to 15 years.

The severity of the disease was looked at in the affected members. This was calculated by the age at present minus the age of onset of disease and also by clinical examination. It was found that there were 6 patients who were mildly affected, 5 were moderately affected while 4 were severely affected.



Group 1b-clinically unaffected

The total number of patients in this group were 70 .There were 36 male patients and 34 females.

The mean age of the patients was about 35 years-Range (6-78 years).

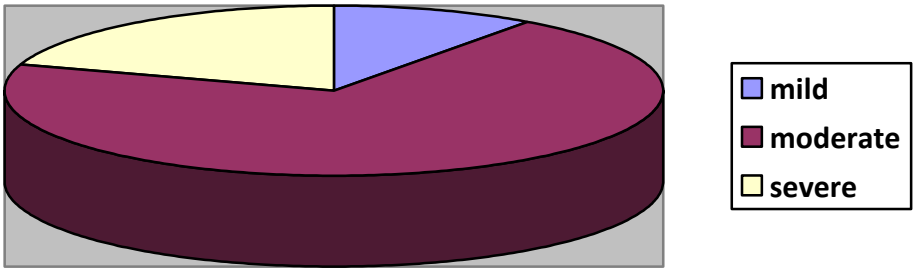
Group 2--hospital visit with positive family history

A total number of 19 patients were taken who presented to the hospital with a family history of ataxia. Of these,10 of them genetic testing positive for SCA-1 were recruited into this study.

The total number of patients was 10 with 5 males and 5 females.
The mean age at presentation was 37 years.

The mean age of onset of symptoms was at **33 years** with **4 years** being the average duration of symptoms.

7 of the patients had only moderate severity of ataxia with 2 severe and 1 mild severe.



age group	Males	females	total	symptomatic	
0-10	1	1	2	-	
10-20	10	7	17	-	
20-30	4	9	13	-	
30-40	3	4	7	2	
40-50	11	9	20	7	
50-60	9	5	14	5	
60-70	2	3	5	1	
70-80	0	1	1	-	

CLINICAL FEATURES

GROUP 1A-CLINICALLY AFFECTED PATIENTS-FAMILIAL

SYMPTOMS

Ataxia was the commonest symptom reported among the affected patients.Out of the 15 affected patients,gait ataxia was reported in all 15 of them.the ataxia was predominantly affecting the gait in the majority of the patients.Ataxia affecting the limbs was seen in 8 of them in the form of limb clumsiness and inco ordination while truncal ataxia was seen in 6 patients.

The ataxia had no diurnal variations in 12 of the 15 patients while 3 of them had a history of increase in symptoms in the dark and on closing the eyes ,thus indicating an additional sensory component.

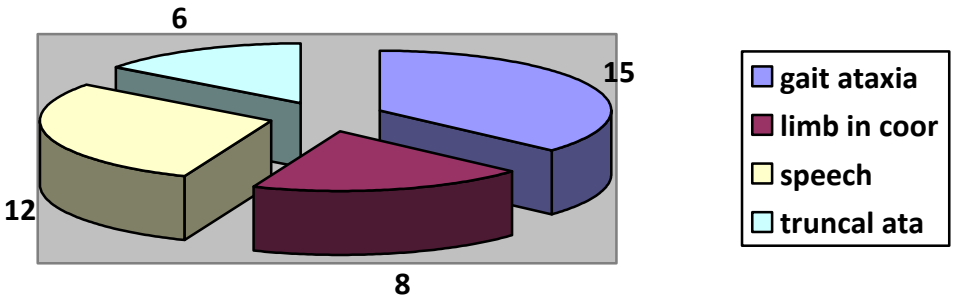
Tremors involving the limbs were seen in 8 of the patients.Of these, all 8 had involvement of mainly the upper limbs.The tremors were predominantly intention tremors which were aggravated on performing various tasks.lower limb tremors were not seen in any of the patients.

Slurred speech was noted in 12 of the patients.This was mainly in the form of

Scanning and ataxia speech.There was no history of fluctuations or diurnal variations of the speech disturbances.

Positive sensory symptoms in the form of tingling and numbness involving the lower limbs were noted in 5 of these patients.there was no history suggestive of sensory loss in the limbs in any of these patients.A history of cramps involving the extremities was elicited in 5 of these patients.

COMMON SYMPTOMS



A history of posturing of the limbs, both upper and lower limbs was seen in 7 of the patients.5 of these had posturing of the upper limbs while 2 had involvement of the lower limbs predominantly.

A history of visual disturbances was seen in 2 of the patients.Of these, 1 had a

history of decreased acuity while another had difficulty in seeing in the dark. There was no history of double vision on lateral or horizontal gaze.

A history of decreased hearing in the ears was obtained in 2 of the patients.There was no ear pain or discharge associated.

A history suggestive of difficulty in swallowing or associated nasal regurgitation was obtained in 5 patients.

Cognitive and behavioural changes history was obtained only in 1 patient.She had a history suggestive of predominantly change in behaviour in the form of becoming more withdrawn and apathetic without significant memory loss or decline.There was no history of apraxias or hallucinations.There was also no history of slowness of movements or frequent falls.

A history of thinning of the limbs was present in 5 of the patients with distal muscles involved predominantly.A history of weakness was obtained in 3 patients with both distal and also axial weakness being present.A history of tightness and heaviness involving the lower limbs was present in about 7 of the patients.There was no history suggestive of clonus.

There was a history of handwriting being affected in 5 of the patients.A history of snoring in sleep and excessive daytime somnolence was obtained in about 2 of the patients.

There was no history of bladder disturbances or migraine headaches.

Positive family history was obtained in all the affected patients.

No history of drug or toxin exposure was obtained in any of the 15 patients.

SYMPTOM CHRONOLOGY

SYMPTOM CHRONOLOGY	
INITIAL SYMPTOMS-WITHIN ONE YEAR OF ONSET	-GAIT ATAXIA -LIMB INCO ORDINATION -SLURRED SPEECH
LATER SYMPTOMS-AFTER ONE YEAR OF ONSET	-LIMB POSTURING -SENSORY SYMPTOMS -SWALLOWING DIFFICULTY

SIGNS

General examination revealed abnormalities in many of the patients.These included facial hemi atrophy confined to the left half of the face seen in 2 of the patients.Also,short neck as defined by the height neck ratio was present in 2 patients.

Icthyosis confined to the lower extremities was present in 2 patients.Vitiligo was seen in 1 of the patients.Furrowing of the forehead was seen in 8 of the patients with wide eyed staring look in 10 of the patients.2 of the patients had contractures involving the ankle joints.

On examination, cardiovascular and abdominal examination revealed no abnormalities in any of the patients.CNS examination showed abnormal MMSE in the 1 patient who had cognitive dysfunction.The areas affected were frontal executive functions and also recall and constructional skills.

Eye abnormalities were seen in patients.These included disc pallor which was present in 2 patients with none of them showing retinal abnormalities.

Eye movement abnormalities were seen in many of the patients.These included slowness of saccadic movements and also broken pursuits which were seen in 10 of the patients.hypermetric saccades which are described in literature were not observed .Lateral gaze nystagmus was seen in 7 patients .Restriction of gaze was seen in 4 patients with upgaze more involved than downgaze.

Fifth nerve involvement in the form of wasting of the temporalis and masseter wasting was present in 11 of the 15.Bifacial weakness was also seen in 6 of the patients. Sensorineural hearing loss was seen in 1 patient.Palatal weakness and depressed gag reflex was observed in 7 patients.Most of these patients were in the advanced stages of the disease.

Slowness of tongue movements was seen in 8 patients.5 of these had evidence of wasting and fasciculations involving the tongue.

Thinning of the limbs was seen in 5 patients with distal wasting more profound.Weakness was seen in the patients.This included distal weakness in 2, both proximal and distal in 1 and axial weakness seen in 1 patient.
Bipyramidal signs including spasticity and extensor plantars were seen in 9 of the patients.

Peripheral nerve involvement in the form of large fiber neuropathy was seen in 6 of the patients.

Involuntary movements in the form of dystonia involving the extremities was seen in 5 of the patients.Axial dystonia was seen in 4 of the patients with involvement of the neck and the tongue predominant.None of the patients had any myoclonus or chorea.

Cerebellar signs in the form of gait and limb inco ordination was seen in all 15

of the patients.Truncal ataxia was seen in 5 of the patients.

GROUP 1B-CLINICALLY ASYMPTOMATIC-FAMILIAL

SYMPTOMS

There were 70 patients in this group.None of these patients were symptomatic for the disease.There was no history of gait and limb inco ordination or slurred speech.

SIGNS

General examination revealed the presence of vitiligo in 1 of the patients.
There were no other neurocutaneous markers.

Disc pallor was seen in 1 patient.Eye movement abnormalities in the form of slow saccades and broken pursuits were observed in 11 patients.Restricted gaze was seen in 1 patient.
Temporalis and masseter wasting was present in 12 of the patients.Tongue wasting and fasciculations were seen in 6 patients.Bipyramidal signs were seen in 6 of the patients.

Evidence of large fiber neuropathy in the form of depressed reflexes was seen in

12 patients.None of the patients had evidence of any sensory loss.

Cerebellar signs in the form of mild clumsiness involving the upper limbs was seen in 3 patients.None of the patients had evidence of gait ataxia or truncal ataxia.

Dystonic posturing involving the upper limbs was seen in 2 patients.

2 of the patients had a history of easy bruising and also gum and abdominal bleeding.They were investigated for the same and found to have von Willebrands disease.They were on conservative treatment for the same.

The patients had the common type 1 variant of Von Willebrands disease where the levels of VW factor are reduced as compared to normal. They normally present with increased susceptibility to bleeding after surgical procedures and trauma. The inheritance is autosomal dominant and linked to chromosome 12.The linkage between SCA and Von willebrands disease has not been postulated and needs further research.

GROUP 2-HOSPITAL VISIT CASES WITH FAMILY HISTORY

SYMPTOMS

Unsteadiness while walking and also slurred speech was seen in all 10 of the patients. 9 of them complained of tremulousness involving the upper limbs. None of the patients had any positive or negative sensory symptoms.

Thinning of the limbs and motor weakness was seen in 3 patients while tightness of the limbs was seen in 6 patients.
None of the patients complained of any posturing of the limbs.None had a history of visual symptoms or cognitive decline

SIGNS

Skin changes in the form of icthyosis was seen in 1 of the patients.hemiatrophy of the face seen in 2 while ankle joint contractures were seen in 1 patient.
Disc pallor seen in only 1 patient while retinal abnormalities were seen in none of the patients.
Eye movement abnormalities were seen in some of the patients. These were in the form of slow saccades in about 8 patients and broken pursuits in about 8 patients.

Lateral gaze nystagmus seen in 8 patients.

Restriction of gaze seen in 4 patients –upgaze more than downgaze.
Temporalis and masseter wasting seen in 4 patients.
Bifacial weakness seen in 2 patients.
Palatal weakness was seen in 2 patients.
Tongue wasting and fasciculations were seen in 2 patients.
Weakness and wasting of the limbs, predominant distal seen in 3 patients.

Bipyramidal signs seen in 6 patients.

Large fiber peripheral neuropathy was seen in 4 patients.

Cerebellar signs were seen in many patients

Gait ataxia was seen in all 10 patients.

Limb tremors were seen in 8 while limb inco ordination was observed in 6 patients.

Extrapyramidal signs were not seen in any of the patients.

PEDIGREE CHARTING AND ANALYSIS

Pedigree charting and analysis was done for both the sporadic and the familial cases. The patterns of inheritance, age of onset of symptoms and age of death of affected members were looked at. Also, the differences in the inheritance patterns with both maternal as well as paternal modes of inheritance were also studied.

The familial cases were divided into a total of 16 families some of whom were related with a total of 85 members being studied. Some of the larger families had about 20 members in each for analysis. Others were part of single unrelated families.

The sporadic cases were unrelated and there were 10 different pedigrees. They were looked at in terms of patterns of inheritance, age of onset and also differences in gender of transmitting parent.

ANALYSIS OF PEDIGREES

-The pattern of inheritance in most of the cases was **autosomal dominant.**

-The pedigrees for upto 3 generations previous to the affected patients could be traced.

-The cause of death for the affected patients seemed to be mainly due to respiratory infections/aspiration pneumonia.

-The phenomenon of **anticipation** was observed in many of the pedigrees studied. The mean age of onset of the affected patients decreased progressively through succeeding generations. This ranged from 60-65 for the first generation affected to 40-45 for the recent generations.

-The interesting point noted in analysis was that the paternally inherited cases had a much **earlier age of onset** as compared to the maternally inherited ones. This has been reported in literature previously. This may be due to the greater instability during paternal transmission as compared to the maternal ones.

	CLINICAL FEATURES
EARLY-MILD TO MODERATE ATAXIA	**-LIMB AND GAIT ATAXIA** **-INTENTION TREMORS** **-SCANNING SPEECH** **-5TH AND 7TH NERVE INVOLVEMENT** **-PYRAMIDAL SIGNS**
LATE-SEVERE ATAXIA	**-AXIAL AND APPENDICULAR DYSTONIA** **-PERIPHERAL NERVE INVOLVEMENT** **-PALATAL WEAKNESS**

-

GENETIC TESTING RESULTS

Genetic testing was done for all the patients in both the groups. This was done with DNA extraction from buccal mucosa cells obtained by buccal washings. DNA amplification and gene characterization was done using PCR techniques.

After the results of the DNA analysis, the number of trinucleotide repeats of certain clinically affected patients was also ascertained. This was done in order to calculate the co relation between the repeat size and the age of onset as well as the clinical severity of the affected patients.

Testing was done for both the groups-the familial as well as the sporadic groups. The results of each were as follows.

GROUP 1-FAMILIAL CASES

These were again further divided into 2 groups-clinically affected and the clinically unaffected.

GROUP 1A-CLINICALLY AFFECTED AND GENETIC POSITIVE

All 15 of the clinically affected patients were genetically positive for SCA-1 mutation. Out of the 15, 13 were heterozygous for the mutation while 2 were homozygous for the same.

The affected patients were from various families in the same locality. There were differences in the clinical presentation, age of onset and also severity of the disease in the affected members of the different families. The clinical features of the affected members have already been described.

GROUP 1B-CLINICALLY ASYMPTOMATIC

These were further divided again into 2 subsets.

Subset 1 were those patients who were clinically asymptomatic and found to be carrying the genetic mutation. These members would theoretically be at risk of manifesting the disease at a later age in life. Some of these patients were found to have subtle clinical signs also, which would be described in detail later.

Subset 2 were patients who were clinically normal as well as genetic testing negative.

SUBSET 1

Of the 21 patients in this subset, there were 9 males and 12 female patients. The mean age in this group was 35 years-range from 13 to 60 years. Although none of these patients were symptomatic, subtle clinical signs were seen in some of these patients. These included:

-Eye movement abnormalities in the form of slow saccades and also broken pursuits were seen in 6 of these patients. However, abnormalities of the disc or the retina were not seen.

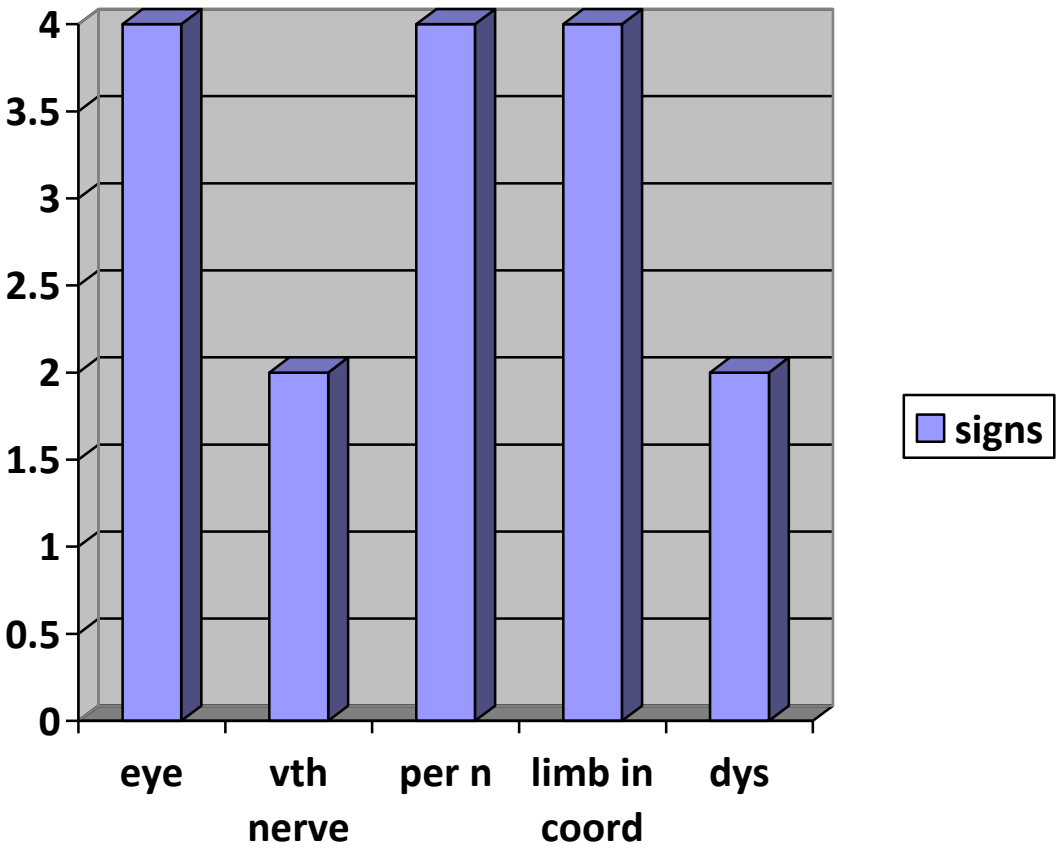
-6 patients had evidence of temporalis and masseter wasting as was seen in many of the affected patients. facial weakness was not seen in any of the patients.

-Evidence of tongue wasting and fasciculations was seen in 4 patients.

-Evidence of bipyramidal involvement was seen only in 2 patients.Peripheral nerve involvement was seen in 5 patients. This was mainly large fiber neuropathy in the form of depressed reflexes.

-Dystonic posturing of the limbs was seen in 2 patient. However, there was no evidence of chorea or myoclonus.

-Evidence of limb inco ordination in the form of mild clumsiness of the upper limb on finger nose finger testing was seen in 4 patients. However, none of the patients had evidence of gait ataxia.



SUBSET 2

Although these were the patients were clinically unaffected and also had tested negative for the mutation, some of them however had subtle clinical features in the form of depressed reflexes, mild limb inco ordination and also temporalis and also masseter wasting present.

These patients are being referred to the main hospital for further evaluation of underlying etiology.

INTRAFAMILIAL DIFFERENCES

Among the affected patients, there were members of different families all in the same locality .There were differences seen in the age of onset and clinical presentation among the various familial groups. These are highlighted below.

There were 15 patients in the affected group. These were divided into various families living in the same region.

Family 1 –largest with 7 affected members

Family 2- 3 members affected

Family 3- 2 members

The remaining 3 members were the only members affected from their families.

DIFFERENCES

1.AGE OF ONSET/INHERITANCE

There were differences between the families with regards to the age of onset and patterns of inheritance.

Family 1 with 7 members had predominantly paternal pattern of inheritance .The age of onset in the first generation was in the fifth decade .However, the next generation had an age of onset in the fourth decade . In this case however, both the mother and the father were affected. This was a double dose of the mutation with earlier age of onset and larger numbers affected. Looking at this family, there were 2 cases with heterozygous inheritance and double dose of mutations which could account for the earlier age of onset.

Family 2 had a maternal pattern of inheritance with age of onset in the fifth decade.

Family 3 had a maternal inheritance with age of onset in the fifth decade.
The remaining 3 members were studied for the pattern of inheritance.
2 of the members had a maternal pattern of inheritance with a later age of onset while the affected member with a paternal inheritance had an earlier age of onset.

PATIENT	AGE OF ONSET-YRS	INHERITANCE
1	30	PATERNAL
2	33	PATERNAL
3	36	MATERNAL
4	38	PATERNAL
5	40	PATERNAL
6	40	PATERNAL
7	40	PATERNAL
8	44	PATERNAL
9	44	MATERNAL
10	45	PATERNAL
11	45	MATERNAL
12	53	MATERNAL
13	53	MATERNAL
14	57	MATERNAL
15	60	MATERNAL

2.CLINICAL FEATURES/SEVERITY

There was no definite difference in the severity of the disease with a range from mild to severe disease.

Regarding the clinical features, there were differences in the families.

Family 1 had almost all members with a characteristic facies. This included a wide eyed staring look along with temporalis and masseter wasting. This was also seen in many asymptomatic individuals. The members with moderate to severe disease also had evidence of bulbar weakness. peripheral neuropathy was also more commonly seen in this family.

Family 2 had features of tongue and limb dystonia. They also complained of cramps and pain in the limbs with aggravation in the night.

Family 3 had one member with advanced disease who had evidence of cognitive dysfunction.

FAMILIAL/HOSPITAL GROUP DIFFERENCES

1.AGE OF ONSET/INHERITANCE

The average age of onset was different in the sporadic and the familial groups.

The age was about 33 years in the sporadic group while it was about 43 in the familial group.
The age of onset was about 10 years earlier in the sporadic group as compared to the familial groups.

Most of the patients in the group had a moderate to severe disease.
The 10 members in the familial group were all from different families.

Looking at the patterns of inheritance, both paternal and maternal patterns of inheritance were seen. however, as seen in the familial group, no differences were seen regarding the age of onset in the paternal and maternal inherited patients.

2.CLINICAL FEATURES

There was a higher proportion of patients who had tremor as a presenting com plaint in the sporadic group. Ataxia and dysarthria were seen in both groups. Temporalis and masseter wasting as well as the wide eyed look were less common in the sporadic group.

Disc pallor as well as lateral gaze nystagmus were seen more in the sporadic group as compared to the familial .

Restriction of vertical gaze was also seen more commonly in the sporadic group.

Distal weakness and pyramidal signs were more common in the sporadic group.

DIFFERENCES

DIFFERENCES	SPORADIC	FAMILIAL
AGE OF ONSET	33 YRS	43 YRS
SEVERITY	MODERATE TO SEVERE	MILD TO MODERATE
INHERITANCE	NO DIFFERENCE	EARLIER ONSET FOR PATERNAL INHERITANCE
TEMPORALIS/MASSETER WASTING	NOT SEEN	CHARACTERISTIC
DISC PALLOR	COMMON	RARE
GAZE EVOKED NYSTAGMUS	COMMON	RARE
GAZE RESTRICTION	COMMON	RARE

INTENTION TREMORS	COMMON	LESS COMMON
PYRAMIDAL SIGNS	COMMON	RARE
PERIPHERAL NEUROPATHY	MORE COMMON	LESS COMMON
BULBAR DYSFUNCTION	LESS SEEN	MORE COMMON

STATISTICAL ANALYSIS

Statistical analysis was done looking for differences in the groups..

1. The patterns of inheritance and age of onset were looked at in the familial kindred. Comparing the maternal and paternal age of onset, it was found that paternally inherited cases had a **significantly** lower age of onset. Mean ages-paternal-38.75 SD-5.1 /maternal-49.71 SD-8.4 **p=0.021**

2. No significant difference was seen in the types of inheritance in the hospital visit group.p=0.69

3. Difference between the homozygous and heterozygous inheritance was looked at and was found to be not significant-p=0.49

4. There was a **significant** difference between the age of onset in the hospital and familial groups .Mean 43.8-familial-SD-8.6 Hospital 32.9 SD 7.9 **p=0.04**

IMAGING FINDINGS

All the patients in the sporadic group as well as some of the patients in the familial group underwent an imaging study-MRI of the brain.

6 patients in the familial group underwent an MRI. According to the disease severity, the findings were as follows.

2 patients with a mild disease-imaging findings showed pure cerebellar atrophy in 1 of the patients while the other patient showed features of OPCA with atrophy of the brainstem as well as the cerebellum.

3 patients with moderate disease-2 showed OPCA pattern while 1 of them showed cerebellar atrophy.

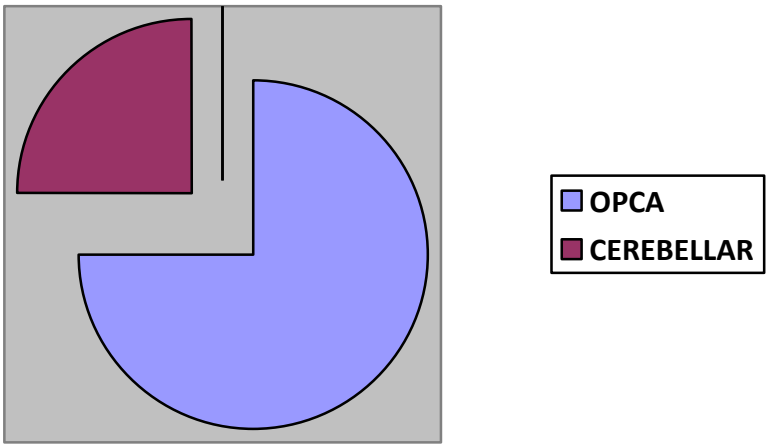
1 patient-severely affected-showed features of an OPCA pattern.

Among the sporadic cases, all of them had imaging done.

The patient with mild disease had only cerebellar atrophy.

Moderate disease -7 patients-6 of them had OPCA pattern with 1 having cerebellar atrophy

Severe disease -2 patients both had OPCA pattern on imaging.



MRS

Magnetic Resonance Spectroscopy –MRS was done in 3 of the familial cases.In the MRS studies done, the voxels were placed in the cerebellum and the pons regions which were compared with the normal areas.

Of the 3 cases, 1 had mild disease while the other two had evidence of moderate and severe disease .

The patient with mild disease had no evidence of any abnormality on the MRS while the ones with moderate and severe disease had the characteristic features of decreased ratios of NAA: creat and also Choline: creat as compared to the normal looking tissue.

Since the number of patients was less, the significance of the above findings needs further studies before comment.

CONDUCTIONS/EVOKED POTENTIALS

EMG and also evoked potentials were done in some of the patients in the study.

EMG STUDIES

Among the familial group, EMG was done in 5 of the affected patients.

4 of them had a normal NCV study

1 of the patients had a mild axonal sensory neuropathy involving the lower limbs

8/10 of the sporadic patients had an NCV study done

6 of them had normal studies.

2 of them had evidence of axonal and demyelinating motor sensory neuropathy involving lower limbs predominantly.

FAMILIAL-NCV

PATIENT	SEVERITY	NCV
1	MILD	NORMAL
2	MODERATE	NORMAL
3	MODERATE	MILD AXONAL SENSORY NEUROPATHY
4	SEVERE	NORMAL
5	MILD	NORMAL

SPORADIC –NCV

PATIENT	SEVERITY	NCV
1	MODERATE	NORMAL
2	MILD	NORMAL
3	MODERATE	AXONAL AND DEMYELINATING MILD NEUROPATHY
3	MODERATE	NORMAL
4	SEVERE	AXONAL AND DEMYELINATING SEVERE NEUROPATHY
5	SEVERE	NORMAL
6	MODERATE	NORMAL
7	SEVERE	NORMAL
8	MODERATE	NORMAL

EVOKED POTENTIALS

5 of the familial group had evoked potentials done

2 of them had abnormal studies

The patient with disc pallor had bilateral optic nerve dysfunction seen on the pattern shift VEP

1 patient had evidence of dorsal cord dysfunction on the tibial SSEP.This was the patient who had symptoms suggestive of sensory ataxia.

Among the sporadic group , 5 had evoked potentials done

Abnormal VEP with bilateral optic nerve dysfunction seen in 1 patient

Prolonged SSEP Tibial with dorsal cord dysfunction seen in 2 patients.

EVOKED POTENTIALS-FAMILIAL

PATIENT	SEVERITY	VEP/SSEP
1	MILD	NORMAL
2	MODERATE	VEP-OPTIC N DYSFUNCTION BILATERAL
3	MODERATE	NORMAL
4	MILD	NORMAL
5	SEVERE	TIBIAL SSEP-DORSAL CORD DYSFUNCTION

SPORADIC

PATIENT	SEVERITY	EVP/SSEP
1	SEVERE	SSEP-ABNORMAL
2	MODERATE	SSEP ABNORMAL
3	MILD	NORMAL
4	SEVERE	ABNORMAL VEP-DISC PALLOR+
5	MODERATE	NORMAL

6. DISCUSSION

DISCUSSION

This study looked at both hospital visit as well as familial cases of SCA-1 .The familial cases were from an area known to contain many affected patients with SCA-1 near Vellore while the hospital cases were inpatients with genetically confirmed SCA-1 admitted in the department of Neurology, CMC, Vellore.

The familial patients were grouped into group 1 with both affected as well as unaffected members included. The sporadic group was classified into group 2 with all members being affected.

A total of 95 patients were studied in this project who were divided into 2 groups. There were 85 patients in group 1 with 45 males and rest females. There were 15 patients among them who were clinically affected-about 18%.70 of them were clinically unaffected.

Among the hospital group, there were 10 patients with both clinical symptoms and genetically proven SCA-1.both males and females were 5 each.

Looking at the clinical features of the affected group of members in group 1, grouped into group 1a.There were 15 members-9 male and 6 female. The mean age of onset of symptoms was about 48 years with the mean duration of

symptoms being about 4 years.6 of the 15 were severely affected with 5 members being moderately affected and 4 having only mild symptoms.

Looking at the hospital group, of the 10 patients, the mean age of onset was 33 years , with 4 years being the duration of symptoms. There is a decade earlier age of onset in the sporadic group as compared to the familial group. The majority of the patients-7 had only moderate severity of symptoms.

CLINICAL FEATURES

Looking at the clinical features in the affected group in the familial patients, it was found that ataxia of gait was the commonest symptom seen in all patients while limb and truncal ataxia were less common. intention tremors, slurred speech and positive sensory symptoms were the less common symptoms seen. The other symptoms seen were involuntary movements with posturing of the limbs, vision and hearing disturbances and mental status changes .Thinning of the limbs and a history of motor weakness were also seen in this group.

Clinical examination revealed many findings. The main findings on general examination were icthyosis and also facial hemi atrophy. There was a characteristic wide eyed and staring look among the affected patients and also furrowed forehead. Another feature seen was the temporalis and masseter

wasting seen in almost 70 % of affected patients.

Cranial nerve findings involved a number of eye findings. These included disc pallor in a few patients. Eye movement abnormalities included slowness of saccades and also broken pursuits seen in the majority of patients. Also, lateral gaze nystagmus and also restriction of vertical gaze were also seen.

Bifacial weakness and also bulbar and palatal weakness was seen in patients with advanced disease. Tongue movements slowness and also tongue fasciculations were seen less commonly.

Evidence of bipyramidal signs were seen in about 60% of the patients. Wasting of the limbs and distal weakness was seen less commonly.

Peripheral nerve involvement was seen in 40% of the patients. This was predominantly large fiber involvement.

Involuntary movements were mainly in the form of dystonia. This was found to involve the peripheries in 33% of patients with axial dystonia seen in about 25%.There were no patients with chorea or myoclonus. Cerebellar signs were seen in almost all patients.

The clinically unaffected patients were 70 in number .None of them had any clinical symptoms. Some of the patients had evidence of subtle clinical

findings. These included eye movement abnormalities seen in about 12% of patients.Also, temporalis and masseter wasting was observed in about 15 % of patients. bipyramidal signs were seen in about 13% of patients. Cerebellar signs and dystonic posturing were seen less commonly.2 of the patients were found to have bleeding manifestations due to von Willebrands disease. The association between the same and SCA-1 has not been elaborated on.

Coming to the sporadic cases, all 10 of them had complaints of gait and limb ataxia. Thinning of the limbs and also limb tightness was seen in some of the patients. On examination, icthyosis and also facial hemiatrophy were seen in about 20% of the patients. Eye signs in the form of slow saccades and broken pursuits and also lateral gaze nystagmus were seen in about 70% of the patients.

Bifacial weakness and palatal weakness were seen less commonly as compared to the familial group. Cerebellar signs were seen in all the patients. Pyramidal signs seen in 60% of patients while 40% of the patients had evidence of large fiber neuropathy. Extra pyramidal signs were not seen in any of the patients.

PEDIGREE ANALYSIS

The pedigree charting and analysis was done for both the sporadic and the familial groups. The patterns of inheritance as well as the age of onset and differences between the sporadic and the familial groups were looked at.

Out of the 85 familial cases, there were 10 families, some of whom were inter related. the sporadic cases were all from 10 unrelated families.

On looking at the pedigrees, the pattern of inheritance was found to be autosomal dominant in keeping with the known facts about SCA-1 inheritance. the pedigrees included details about 3 generations .

The cause of death of affected members in previous generations seemed to be respiratory with bulbar dysfunction and aspiration pneumonia.

There were 2 additional phenomena observed with the pedigree charting.
The first observation was that of anticipation-the age of onset of the affected members were progressively decreasing in succeeding generations. This changed from 60-65 in the first generations to about 40-45 in the third. This is in keeping with the phenomena seen in trinucleotide repeat disorders.

The second observation was that maternally inherited cases seemed to have a later age of onset while those inheriting the mutation from paternal inheritance were affected at an earlier age. This could be in keeping with the greater genetic instability during paternal transmission. This in also in keeping with earlier studies some of which have found the same association.

The clinical signs and severity of the disease were looked at. It was found that the cases with mild ataxia were found to have gait and limb ataxia along with speech disturbances and intention tremors. Pyramidal signs were also an early sign. the later onset signs were bulbar weakness and also peripheral dystonia.

GENETIC TESTING RESULTS

Genetic testing was done in both the groups. this was done using DNA extracted from buccal smears. Genetic testing was done for both SCA-1 as well as SCA-2. The number of trinucleotide repeats in the affected patients was also looked at. This was done in order to look at the co relation co efficient between the number of repeats and the age of onset and severity of the disease. Genetic testing was also done to confirm the genotype of the SCA-1 sporadic cases.

The testing done in group 1 showed positive results for SCA-1 in all 15 of the patients.13 of them were genetically heterogenous while 2 were homogenous for the mutation.

Out of the 75 patients who were clinically unaffected, 21 of them tested positive for the mutation. These were the genetic testing positive and clinically unaffected patients. On looking at these patients in detail, subtle clinical findings were found. These included the following.

Eye movement abnormalities seen in 25 % of these patients in the form of slow saccades and also broken pursuits. Temporalis and masseter wasting was also seen in about 25% of patients. Limb dystonia and tongue fasciculations were seen in only a few patients.

25% of patients had evidence of peripheral neuropathy and also evidence of cerebellar signs in the form of limb inco ordination.

The differences between the different families was looked at. the patterns of inheritance were studied. It was found that the families with maternal patterns of inheritance had a later age of onset while those with paternal pattern of inheritance had an earlier age of onset comparatively.

Regarding the clinical features, comparing the different families, one set of patients had a characteristic phenotype with temporalis and masseter wasting along with peripheral neuropathy and also bulbar dysfunction. The other family had evidence of peripheral dystonia along with positive sensory symptoms ,predominantly nocturnal. only 1 patient had evidence of cognitive dysfunction.

Comparing the differences between the hospital and the familial cases, it was seen that the onset of symptoms was about 10 years earlier in the sporadic group as compared to the famial-33 versus 43.The majority of patients in the sporadic group had moderate to severe disease. There were no major differences between the groups regarding the patterns of inheritance.

The sporadic cases had a higher number of patients with intention tremors, gaze evoked nystagmus as well as restriction of vertical gaze compared to the familial cases. distal weakness, peripheral neuropathy as well as disc pallor were also more commonly seen in the sporadic group.

STATISTICAL ANALYSIS

The analysis showed that there was a significant difference in the age of onset in the paternal and maternal cases in the familial group but not in the sporadic group. This could be explained by the greater genetic instability during paternal meiosis .

There was also a significant difference between the ages of onset of familial and hospital cases which may be due to small numbers and also referral bias.

No difference was made out between homozygous and heterozygous inheritance.

IMAGING

6 of the patients in the familial group underwent an MRI of the brain. Of these, 66% had features of OPCA on imaging including involvement of the brainstem and also the cerebellum. The rest of them, mainly the mildly and moderately affected patients had evidence of pure cerebellar atrophy.

Out of the 10 sporadic cases, 80% had features of an OPCA pattern while the remaining had pure cerebellar atrophy.
Milder cases had pure cerebellar atrophy while moderate to severely affected cases had OPCA pattern.

MRS

Magnetic Resonance Spectroscopy was done in a few patients. The findings seen in the moderate to severely affected patients was a reduction in the NAA:Creat and also Choline :creat ratios in the cerebellum and also the pons as compared to normal regions.

EMG/NCV

-NCV study was done in 5 of the familial cases. Of these, only 1 patient had evidence of a predominant sensory neuropathy involving the lower limbs.
In the sporadic group, out of 6 patients, only 2 had evidence of a sensorimotor neuropathy ,both axonal and demyelinating predominantly involving the lower limbs.

EVOKED POTENTIALS

-5 of the patients in the familial group had evoked potentials done.2 of these were abnormal.1 with bilateral optic nerve dysfunction and abnormal VEP with 1 abnormal tibial SSEP with dorsal cord dysfunction.

Of the 10 patients in the hospital group, only 3 had abnormalities.1 with an abnormal VEP and 2 with dorsal cord dysfunction and abnormal tibial SSEPs. Patients with history of sensory ataxia had electrophysiological co relate of abnormal SSEPs.

FURTHER PLANS

The number of trinucleotide repeats would be looked at in the affected individuals and co relation would be done with the severity of the disease and age of onset .comparisons would also be done between the familial and hospital groups.

Genetic counselling would be offered to affected families.

Occupational and physiotherapy to affected members for enhancing the quality of life.

Improvement of socio economic factors.

Holistic care to entire community.

7. CONCLUSIONS

- This study looked at both hospital and familial cases with SCA-1.A total of 95 cases were recruited into the study.
- The hospital cases were recruited from inpatients in CMC hospital, Vellore positive for SCA-1 mutation and were 10 in number totally.
- The familial cases were recruited from an area endemic for SCA-1 near Adigambarai, vellore. There were 85 members recruited with a male preponderance.
- 15 of the 85 members in the familial population were clinically affected- about 18%
- The age of onset of symptoms in the sporadic group was about 33 years with 4 years being the mean duration of symptoms being about 4 years. The age of onset in the familial cases was about 43 years. The later age of onset in the familial group could be explained by the referral bias.
- Gait ataxia was the commonest and also the first symptom noted in both the groups. Limb inco ordination and also slurred speech were less common. Bulbar symptoms and involuntary limb posturing were less common.
- The clinical features of both the hospital and the familial groups were compared. The familial group had certain phenotypic features

characteristic .These included wide eyed staring look along with evidence of temporalis and also masseter wasting. Certain kindreds also showed evidence of limb dystonia and also bulbar weakness in later stages.

- The hospital cases showed greater incidence of intention tremors of the limbs along with bipyramidal signs and also eye signs including gaze evoked nystagmus and also restriction of vertical gaze.
- Both groups showed features of hypometric saccades and broken pursuits along with evidence of peripheral neuropathy.
- Detailed pedigree charting was done in the affected members and also their relatives. Certain facts were confirmed with the same. The pattern of inheritance was found to be autosomal dominant. The phenomenon of anticipation was seen with the age of onset being progressively lower in succeeding generations. Another feature seen was the earlier age of onset seen in cases with paternal inheritance. This could be explained by the greater genetic instability seen with paternal mutations.
- Genetic analysis was done using buccal DNA extraction techniques.On analysis of the results,all 15 of the clinically affected patients in the familial group were positive for SCA-1 as were the 10 cases in the sporadic group.
- Of the 70 asymptomatic patients in the familial group, about 21 of them were positive for the genetic mutation for SCA-1.some of them showed subtle clinical features including temporalis and masseter wasting along

with eye signs and also mild limb inco ordination. These patients need to be followed up for a longer time for noting the age of onset and clinical features.

- Both intrafamilial differences as well as differences between the hospital and the familial groups were seen with regards to the clinical features.Phenotypic heterogeneity was observed.
- Paternally inherited cases had a significantly lesser age of onset in the familial group.
- No significant difference was found in heterozygous versus homozygous inheritance.
- Imaging done showed features of OPCA pattern in the majority of the patients with a few showing evidence of only pure cerebellar atrophy. The OPCA pattern was more common in those with moderate to severe disease with cerebellar atrophy in the milder group.
- MR spectroscopy done showed reduced levels of NAA and also choline in the cerebellum and the pons.
- NCV studies showed features of axonal and demyelinating sensorimotor neuropathy in patients with moderate to severe disease.
- Abnormal VEPs and also Tibial SSEPs were also seen in a few of the patients with advanced disease. This was seen in patients with complaints of sensory ataxia thus offering an electrophysiological co relation

- Further studies to look at the number of tricucleotide repeats and their clinical correlation with age of onset and the severity of the disease would be done at a later stage.

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IMAGES

1. PATHOGENESIS OF SCA

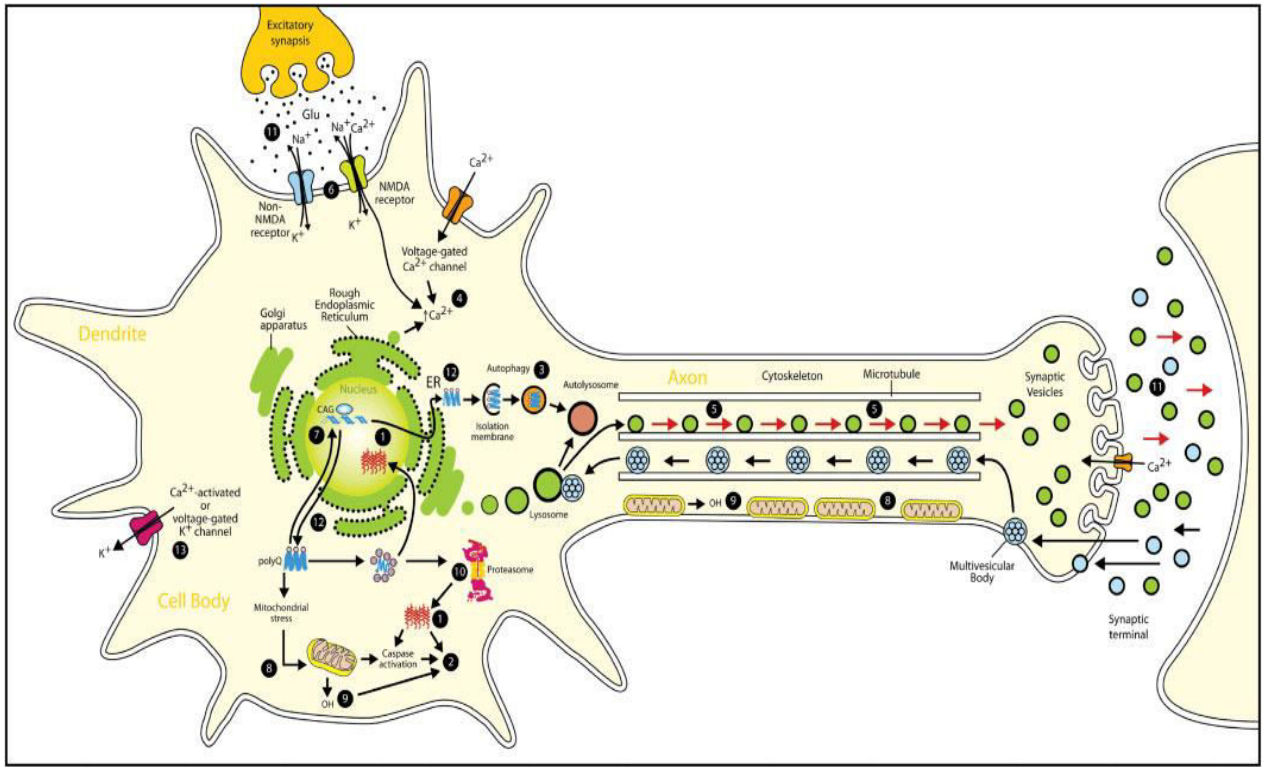
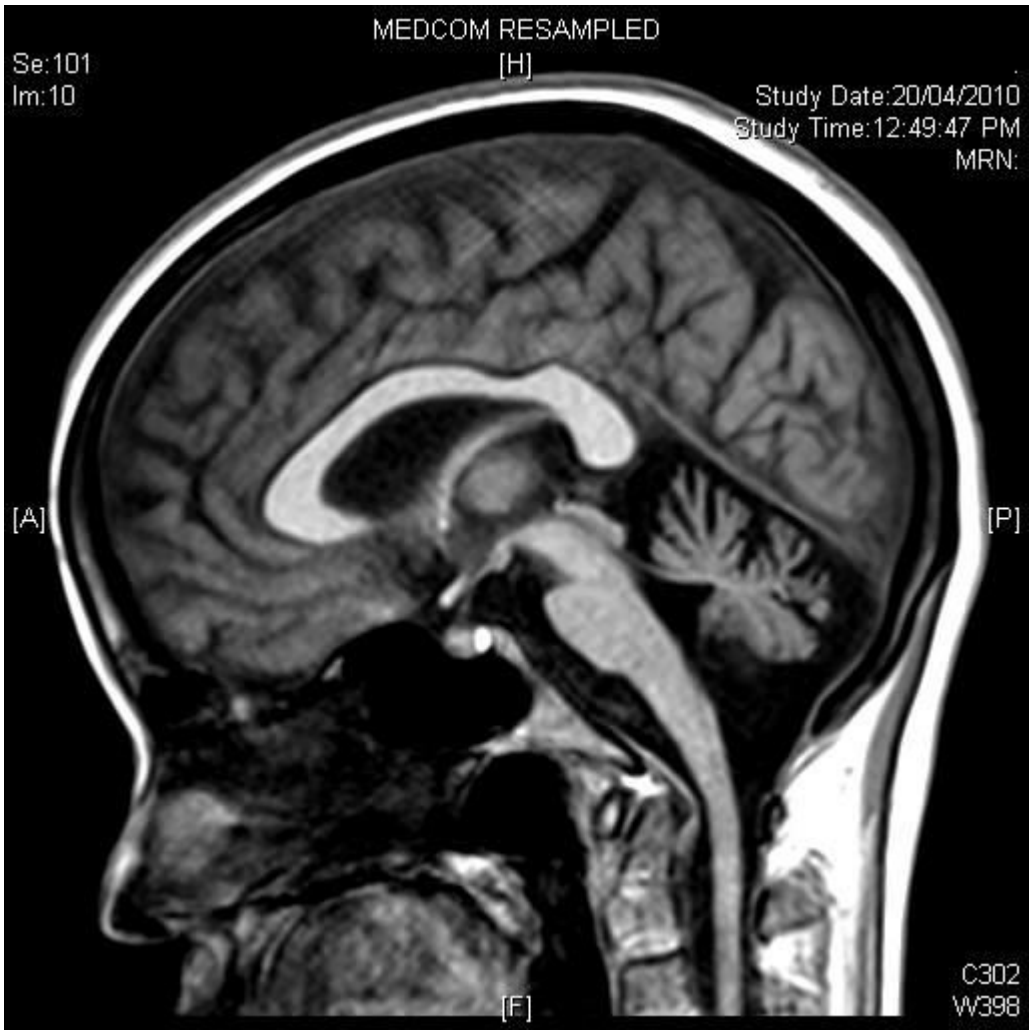


FIG-Molecular mechanisms of neurodegeneration in spinocerebellar ataxias. 1, aggregation; 2, apoptosis; 3, autophagy;
4, Ca2+ homeostasis alterations; 5, disruption of axonal transport and vesicle trafficking; 6, excitotoxicity; 7, interference with gene
transcription; 8, mitochondrial impairment; 9, oxidative stress; 10, alterations of proteasome degradation; 11, synaptic dysfunction;
12, unfolded protein response (UPR); 13, potassium channel dysfunction; Ca2+, calcium ions; ER, endoplasmic reticulum; Glu, glutamate;
K+, potassium ions; Na+, sodium ions; Q, glutamine; Ub, ubiquitin

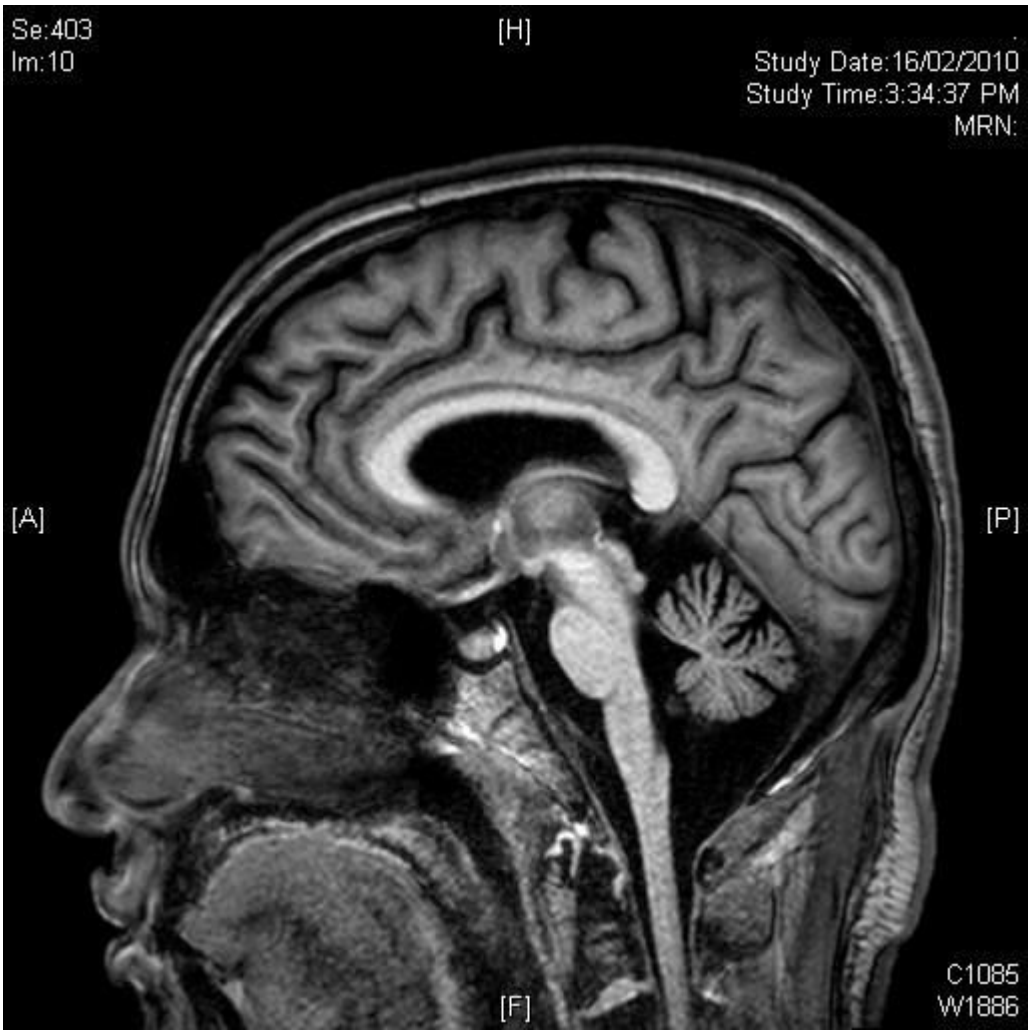
2.MRI IMAGES



OPCA PATTERN-atrophy of the pons and cerebellum-sagittal view

OPCA PATTERN-brainstem and cerebellar atrophy-axial view

CEREBELLAR ATROPHY

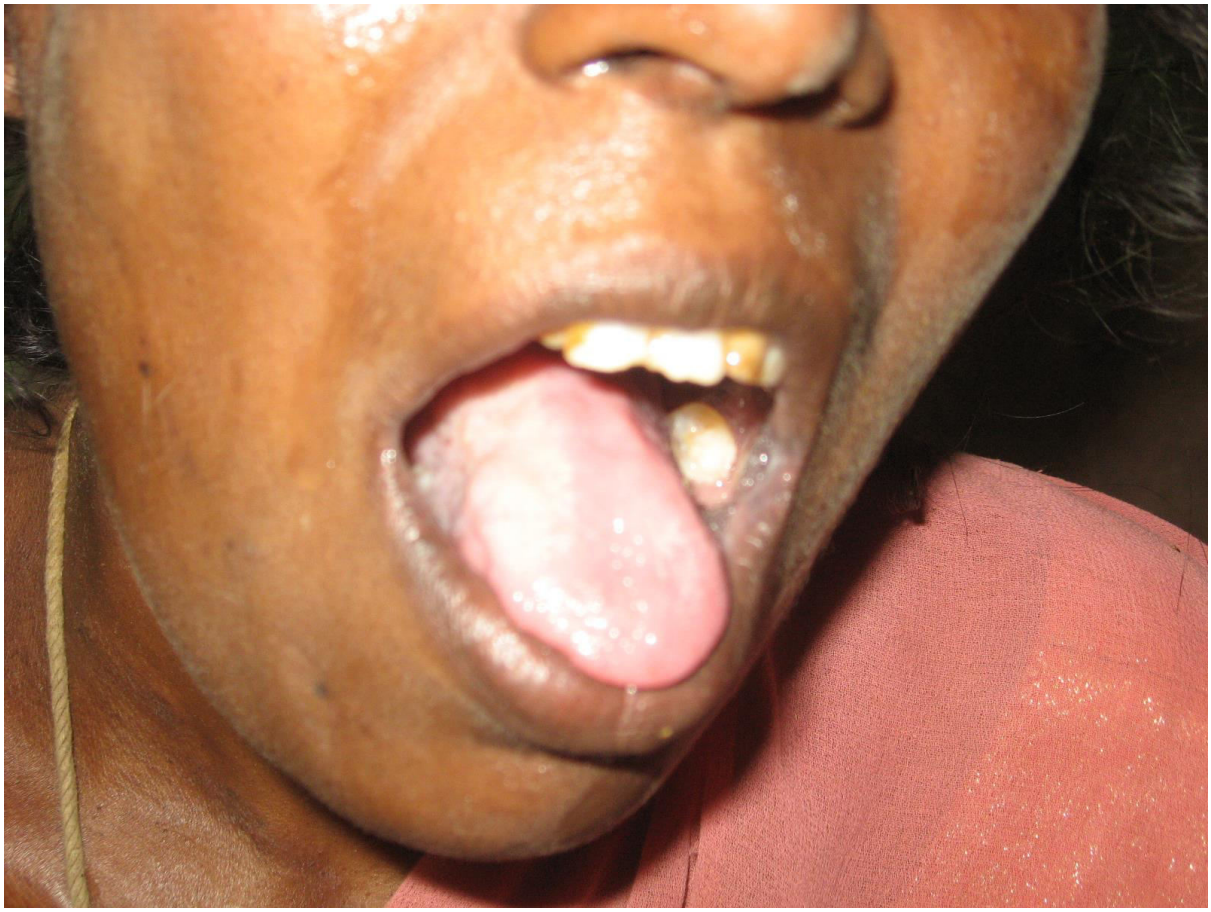


CLINICAL PHOTOGRAPHS

STARING LOOK with wide palpebral fissures

TEMPORALIS/MASSETER WASTING-familial group

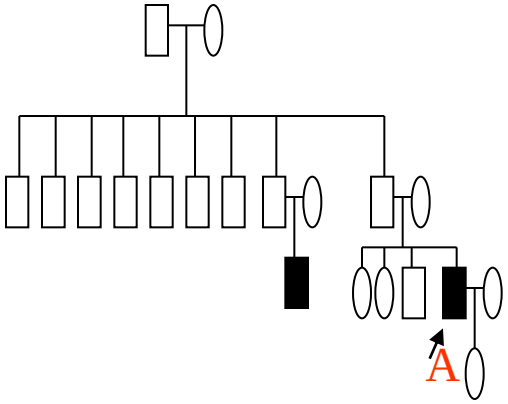
TONGUE WASTING-patient with bulbar dysfunction



LIMB DYSTONIA

STARING LOOK/TEMPORALIS WASTING-familial group

ANNEXURES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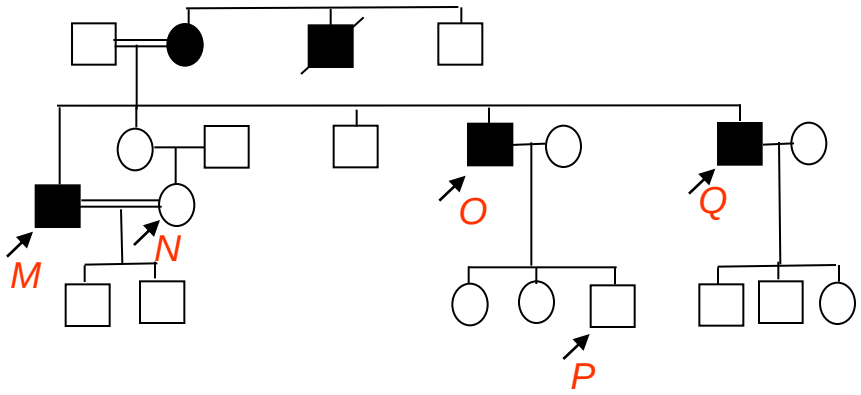
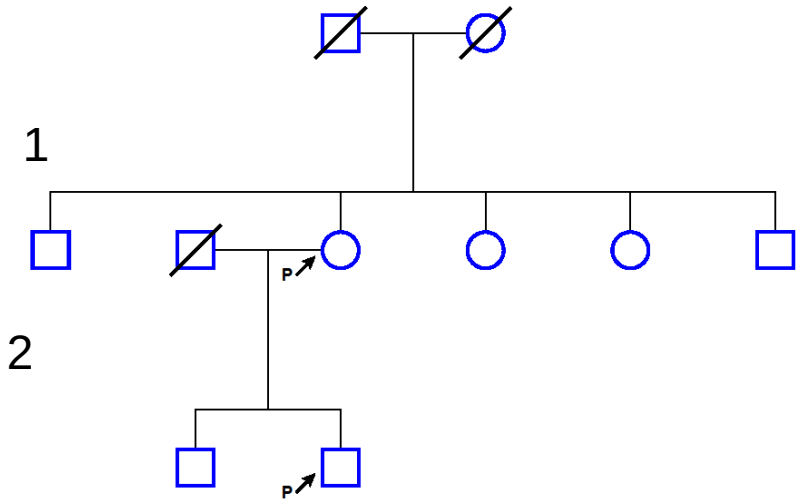

M
N
O
P
Q

Family dhanabhagayam



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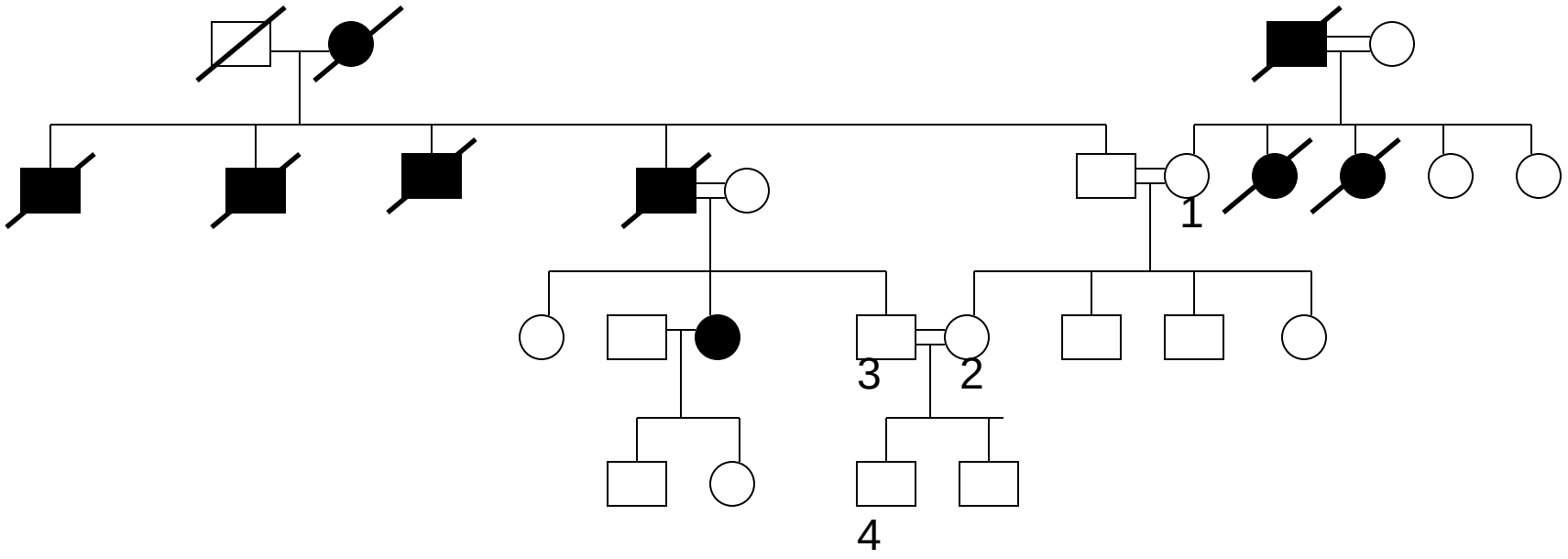
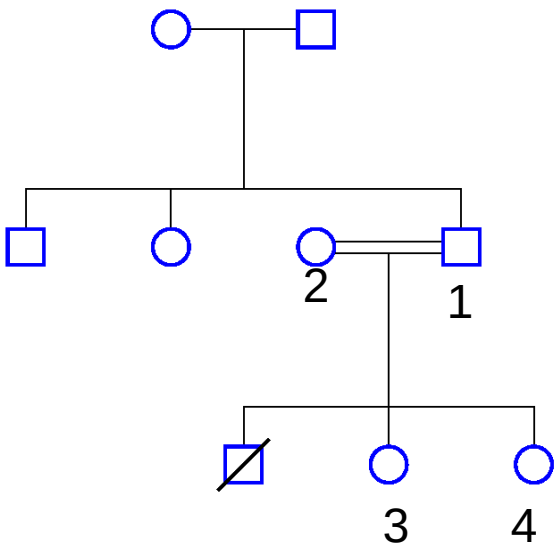
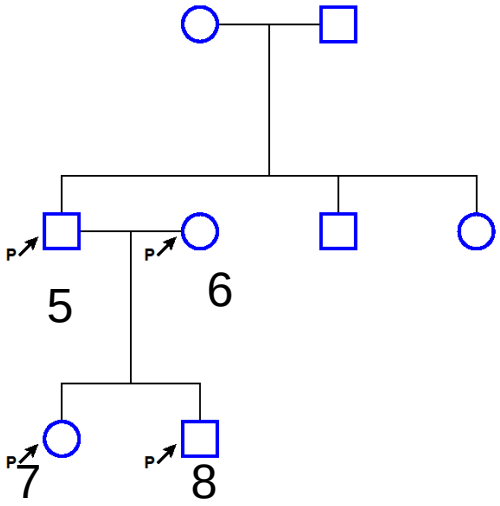
Family Kanthamma



Family parasuraman



Family thirupanandam



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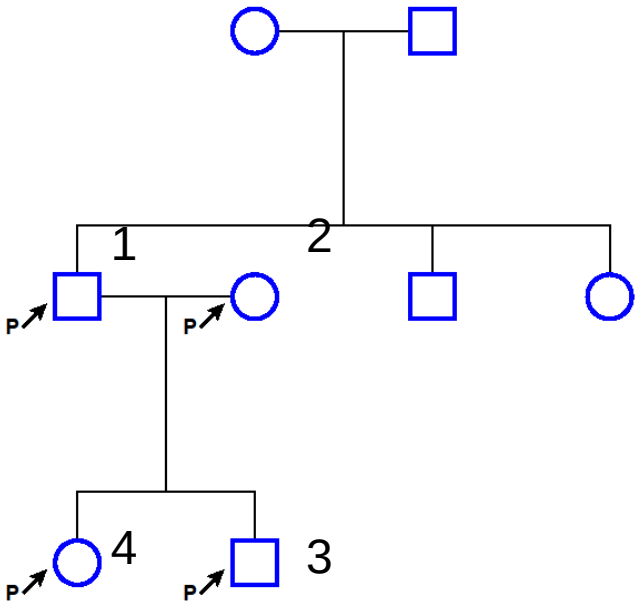
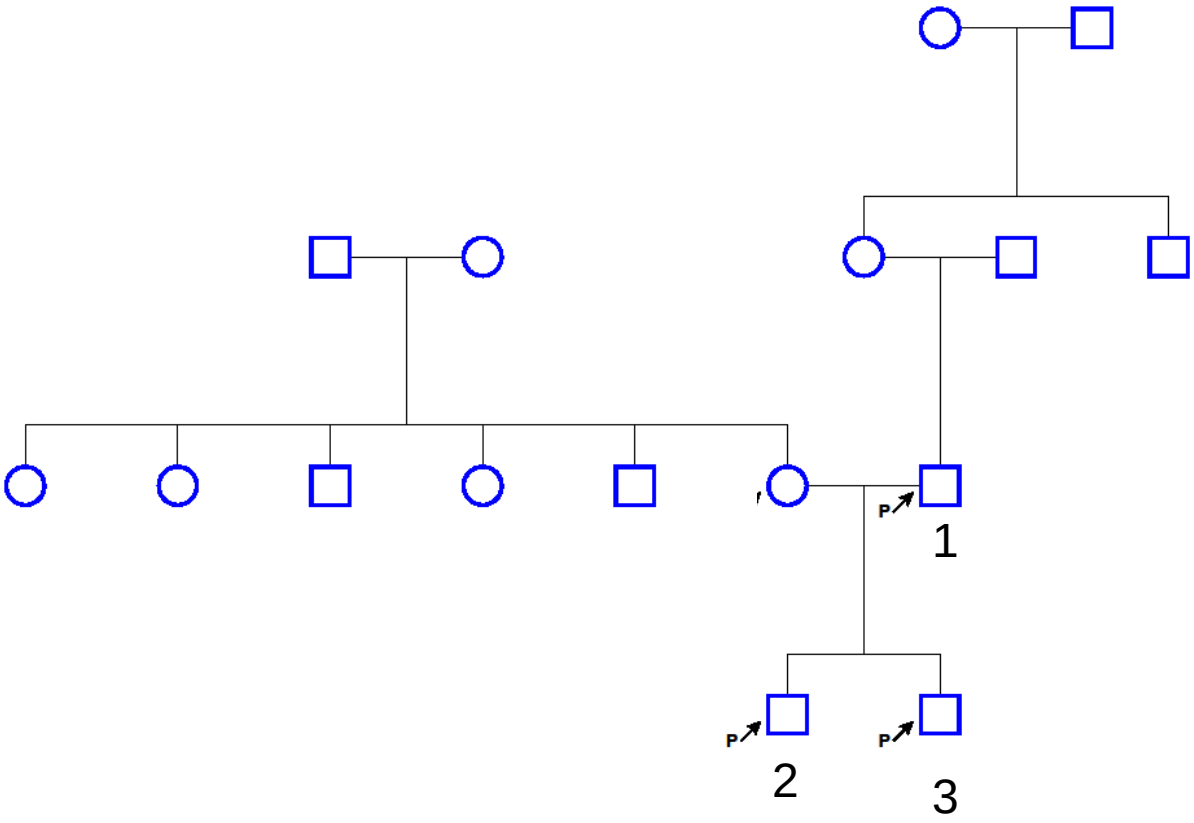
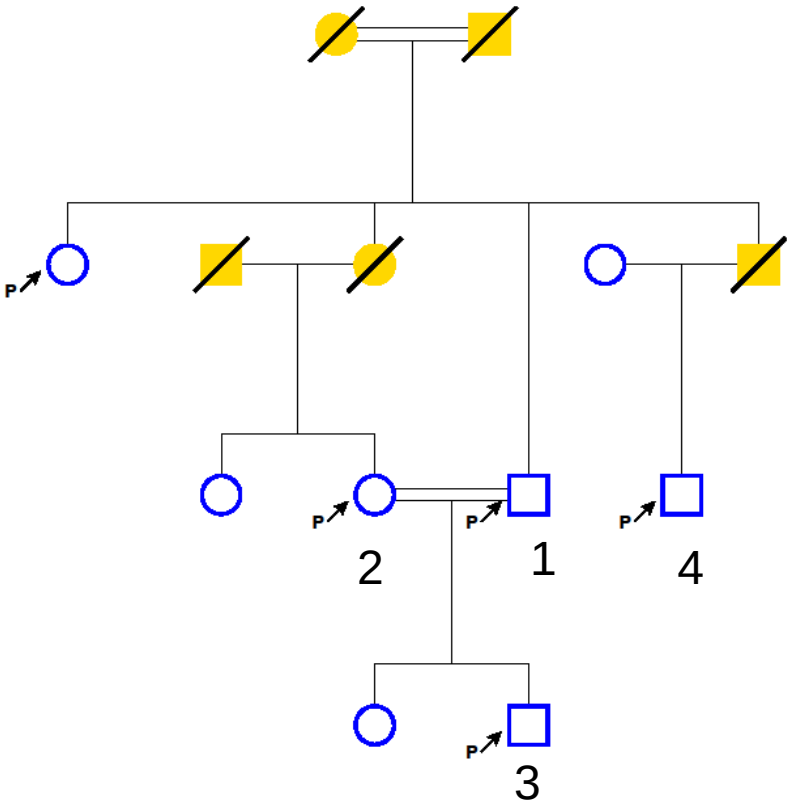


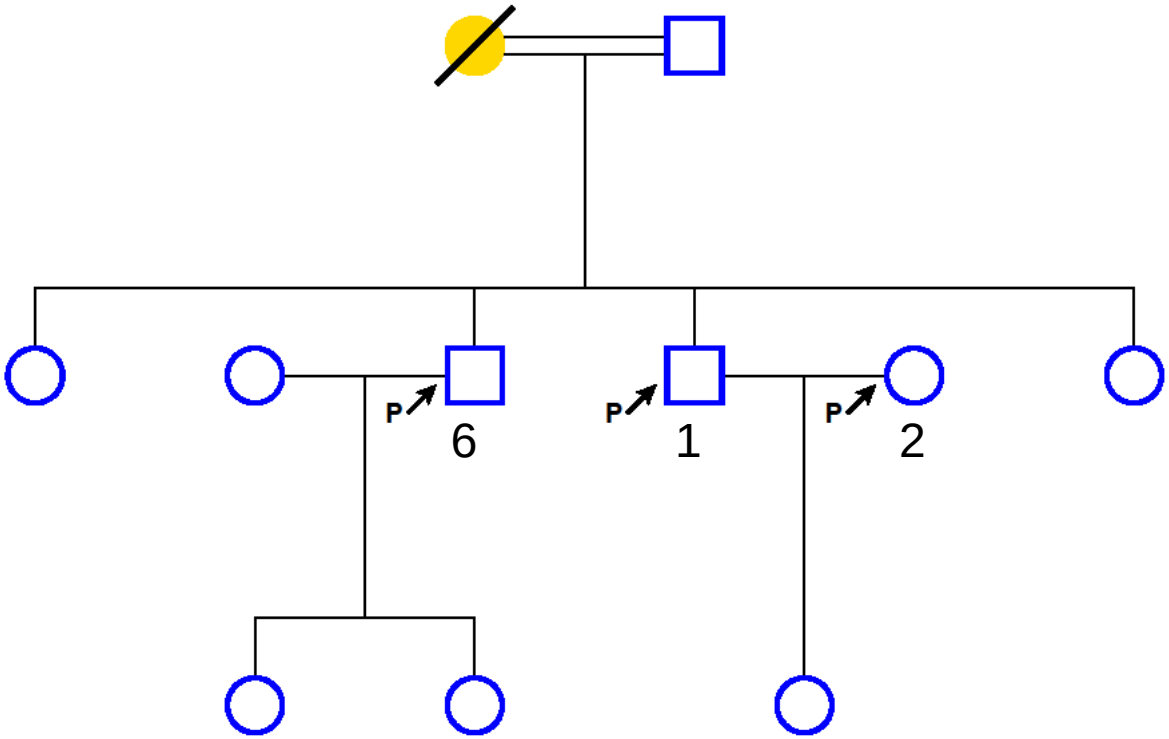
Family kuselan



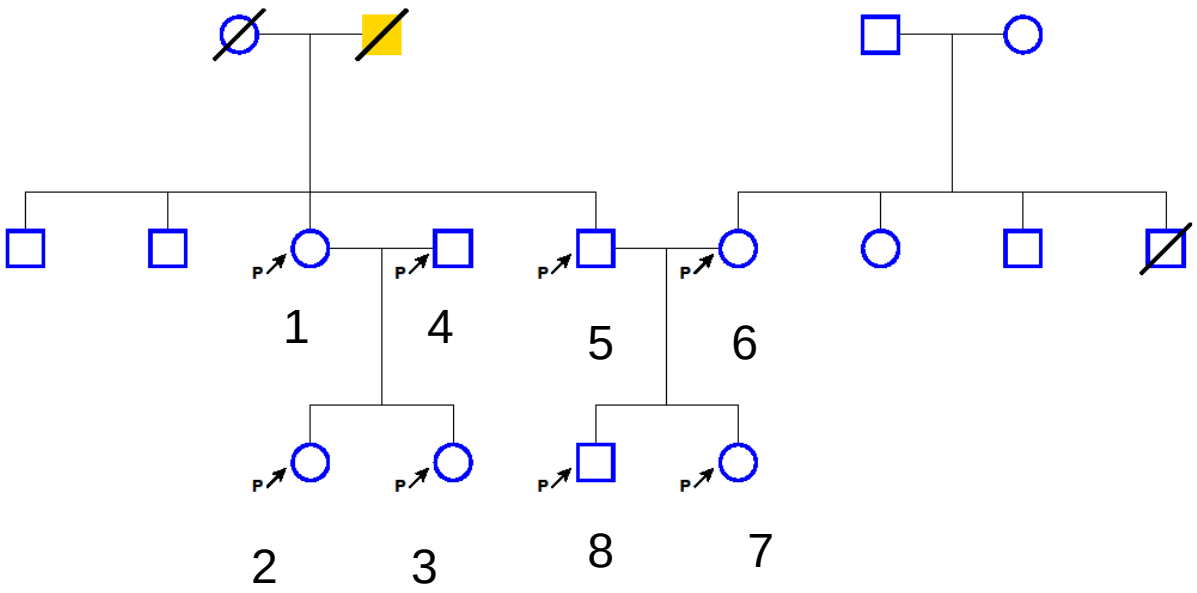
Family manoharan



Family natarajan



Family pattu



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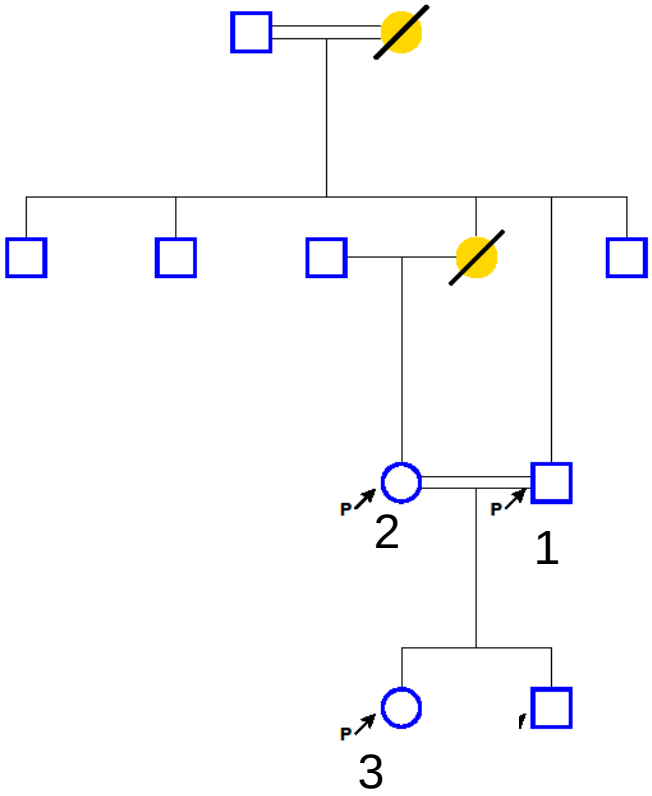
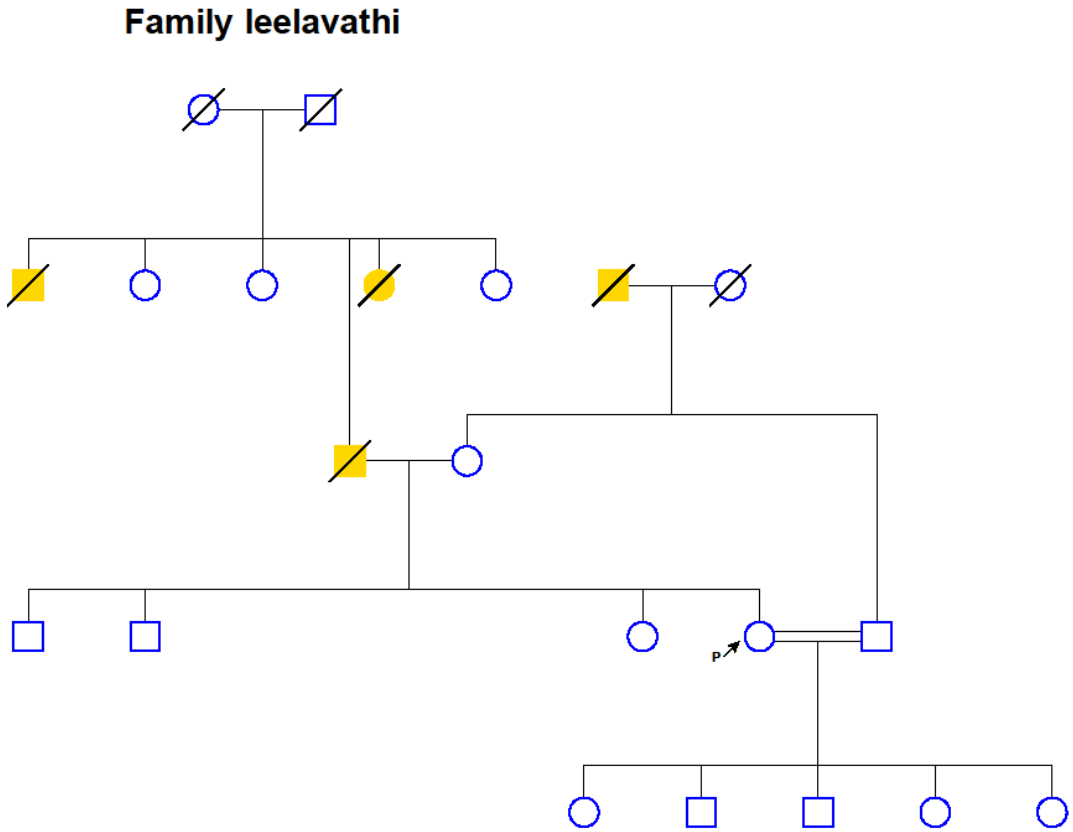
Family prabhu

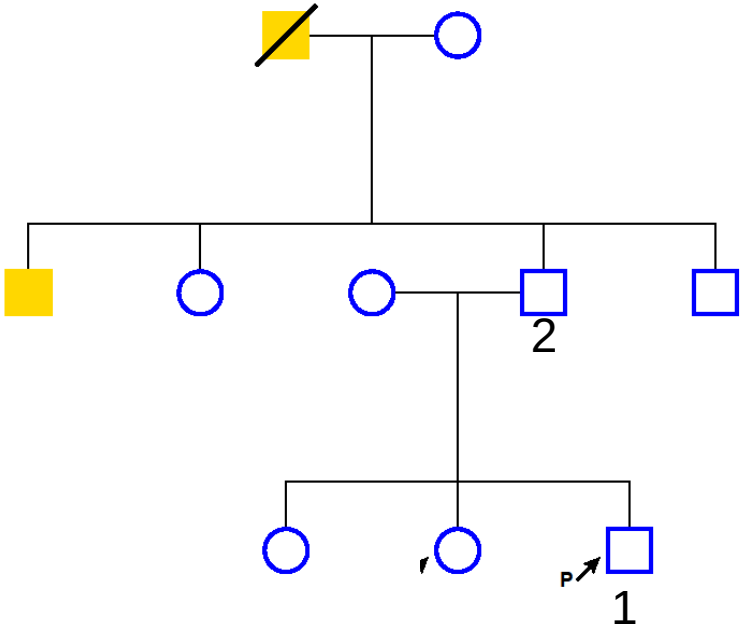




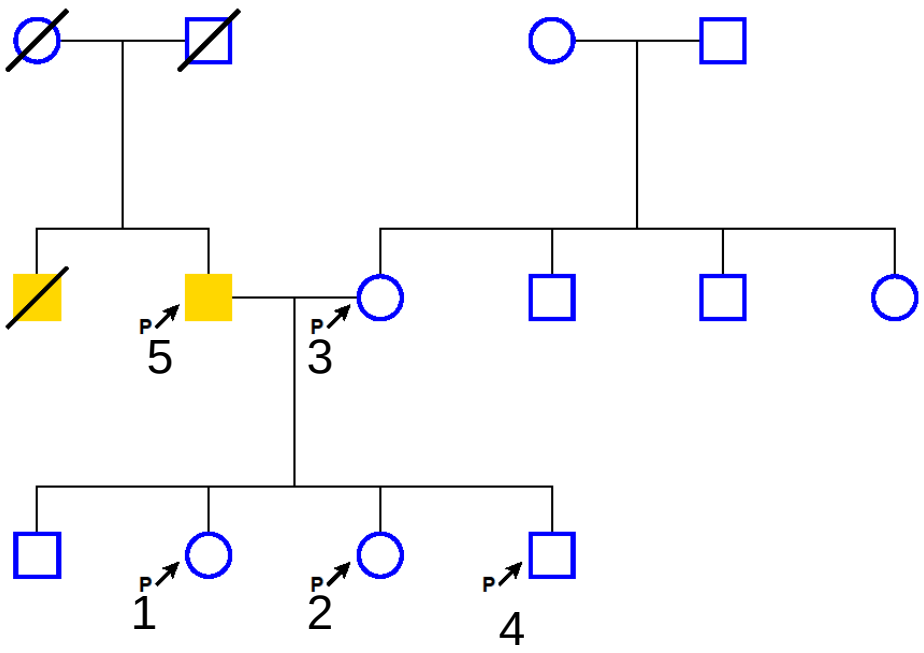
PC

Leelavathi,F,40Y

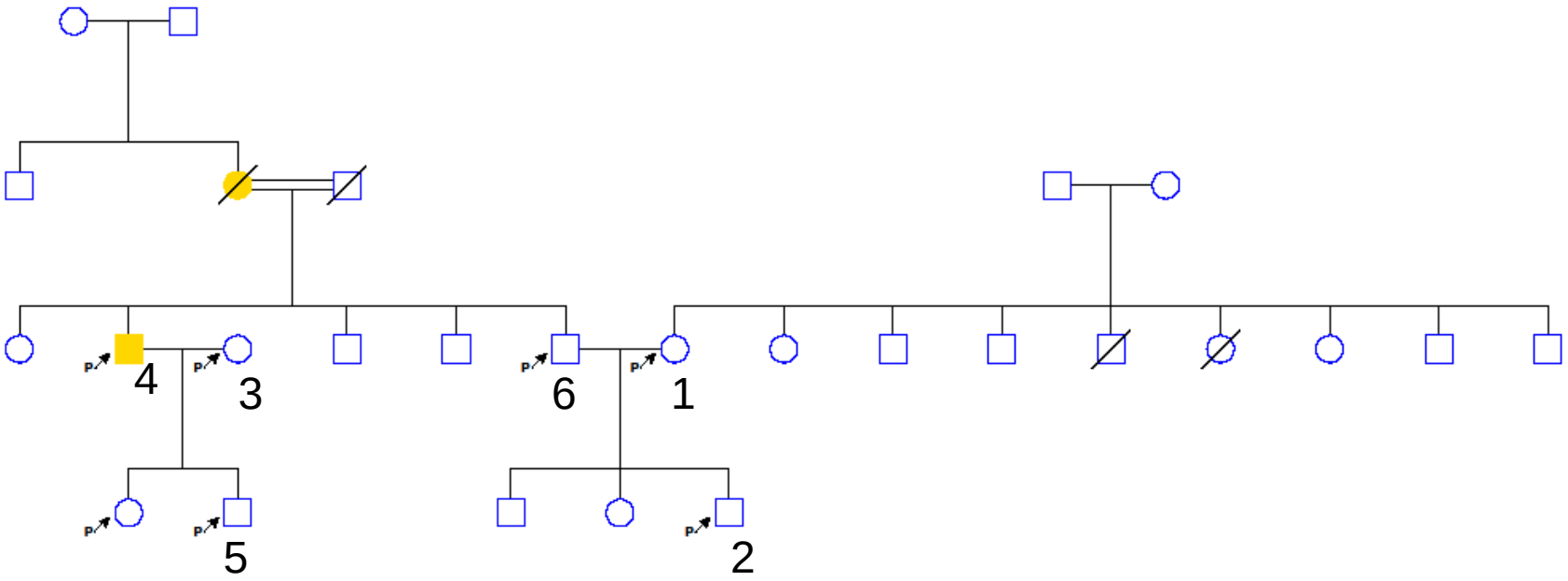
Family purushotaman



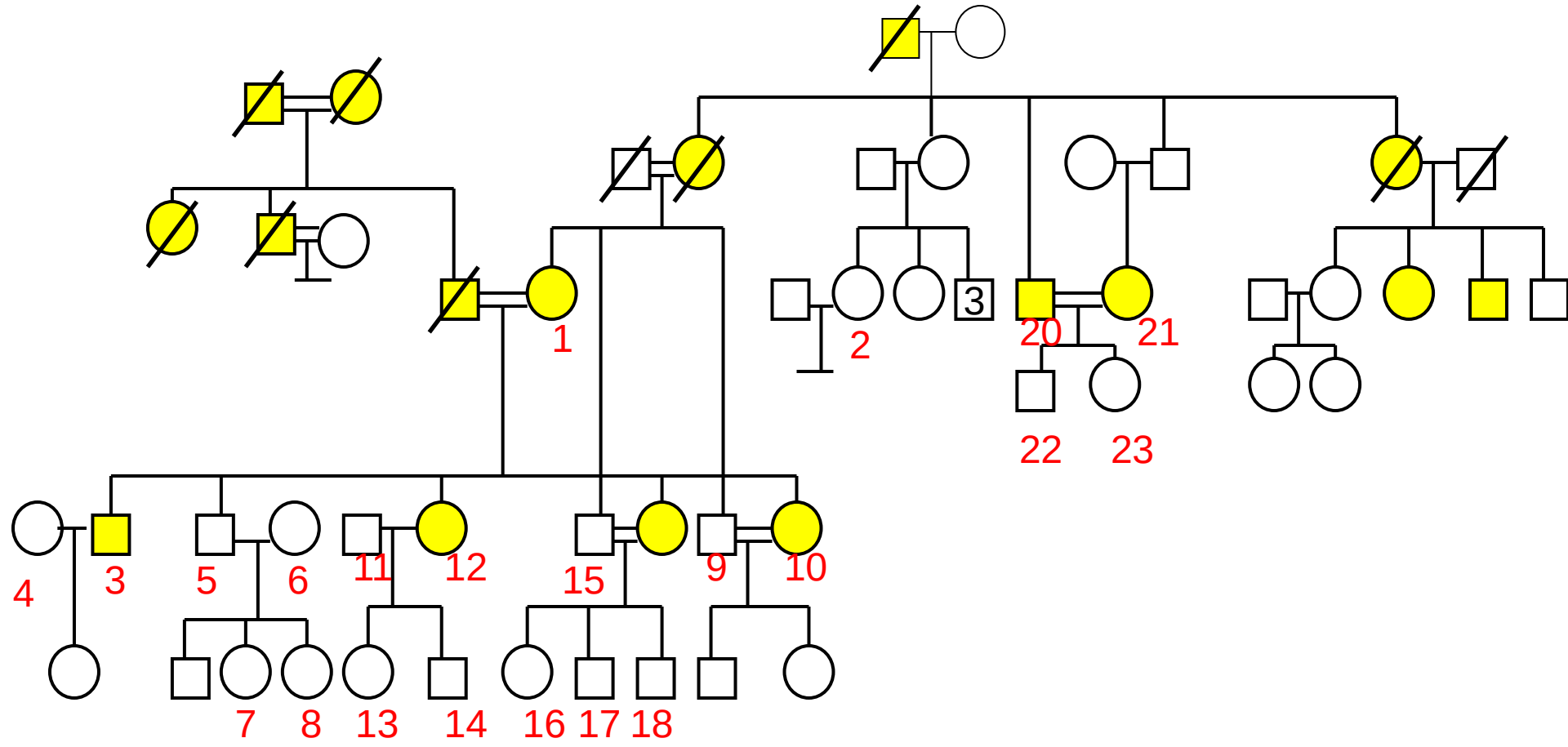
Family ramamurthy



Family vinayakam



FAMILY SETU



name	age	sex	clin aff	Gen test	age at ons	durat	sever	ataxia
kalaiselvi	43	f	y	sca 1	40	3	sev	y
nirmala	46	f	y	sca1	39	6	sev	y
sukla	37	f	y	sca1	32	5	mod	y
priyanka	21	f	y	sca1	18	3	mod	y
jaglal	20	m	y	sca1	19	1	mod	y
prasath	40	m	y	sca1	38	2	mod	y
atanu	39	m	y	sca1	37	2	mild	y
masthan	47	m	y	sca1	37	10	mod	y
latha	35	f	y	sca1	34	1	mod	y
prakash	38	m	y	sca1	35	3	mod	y
	36.6				32.9	3.6		

dysarthria	tremors	cramps	dystonia	visual	cognition	handwrit	sleep	migraine
y	y	n	n	n	n	n	n	n
y	y	n	n	n	n	n	n	n
y	y	n	n	n	n	n	n	n
y	y	n	n	n	n	n	n	n
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y	y	n	n	n	n	n	n	n
y	y	n	n	n	n	n	n	n

bladder	hemiatrop	ichthyosis	short neck	contractu	mmse	pale disc	retina	slow sacc
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n	n	n	n	n	n	n	n	y

pursuits	gaze rest	5th n	7th n	8th n	9/10th	12th n	wasting	weakness
y	y	n	n	n	n	n	n	n
y	y	y	y	n	y	n	y	y
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y	y	n	y	n	n	y	n	n
y	n	n	n	n	n	n	n	n

pyramidal	per nerve	dystonia	chorea	myoclonus	gait ataxia	tremors	fascicula	extrapyr
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y	n	n	n	n	y	y	n	n
y	n	n	n	n	y	n	n	n

inco ordina
y
y
n
y
y
n
y
y
y
y

name	age	sex	clin aff	Gen test	age at ons	durat	sever	ataxia
settu	54	m	y	y	53	1	mild	y
elumalai	34	m	y	y	33	1	mod	y
ramalingar	55	m	y	y	45	10	sev	y
ramamurth	55	m	y	y	40	15	mod	y
malarvizhi	46	f	y	y	36	10	sev	y
natarajan	58	m	y	y	57	1	mild	y
sathyavani	43	f	y	y	38	5	sev	y
kalaivani	41	f	y	y	40	1	mod	y
dhandapar	31	m	y	y	30	1	mild	y
damodarar	55	m	y	y	53	2	mod	y
vetrivel	38	m	n	y				n
vinod	15	m	n	y				n
loganathan	50	m	n	y				n
devi	22	f	n	y				n
diwakar	10	m	n	n				n
selvi	38	f	n	n				n
prasad	18	m	n	n				n
vanitha	50	f	n	n				n
vinayagam	65	m	n	n				n
jyothi	42	f	y		40	2	sev	y
asokan	47	m	y		45	2	mod	y
indrani	65	f	y		60	5	mild	y
malarvizhi	45	f	y		44	1	mild	y
rajendran	45	m	y		44	1	mild	y
selvam	42	m	n					n
kamaraj	47	m	n					n
dhanabagy	70	f	n					n
#kalpana	35	f	n					n
#kanthamn	60	f	n					n
dhanalaksh	60	f	n					n
rajendran	20	m	n					n
settu	45	m	n					n
divya bhara	11	f	n					n
shubha	21	f	n					n
masilamani	50	m	n					n
suresh	13	m	n					n
priya	**17**	f	n					n
parasurama	60	m	n					n
yuvaraj	19	m	n					n
jayasuriya	9	m	n					n
thiruppan	40	m	n					n
priyanka	6	f	n					n
vimala	55	f	n					n
dili rani	15	f	n					n
neelavathi	40	f	n					n
venda	28	f	n					n

nalini	19	f	n			n
purushotta	20	m	n			n
mani	60	m	n			n
vijkumar	23	m	n			n
barath	21	m	n			
poovarasar	12	m	n			
sivagami	45	f	n			
naresh	16	m	n			
prabhu	21	m	n			
manogaran	41	m	n			
sivalingam	58	m	n			
elavarasi	48	f	n			
santha	59	f	n			
revathi	23	f	n			
thanjamma	38	f	n			
dorai	70	m	n			
malliga	39	f	n			
bhaskar	27	m	n			
deepak	14	m	n			
indira	45	f	n			
ranu	70	f	n			
suresh	13	m	n			
kuselan	41	m	n			
meghnath	13	m	n			
kalairasi	13	f	n			
subramani	45	m	n			
vijayashan	23	f	n			
amudhu	28	f	n			
venkatesar	55	m	n			
natarajan	45	m	n			n
malliga	25	f	n			n
pavithra	17	f	n			n
elumalai	46	m	n	n		n
gomathi	25	f	n			n
vennila	21	f	n			n
bhavani	15	f	n			n
pattu	76	f	n			n
mani	60	m	n			n
kasthuri	52	f	n			n
meghala	16	f	n			n
suchita	5	f	n			n
rajeswari	21	f	n			
sugasini	16	f	n			
anbu	20	m	n			
pattu	70	f	n			
lalitha	60	f	n			

dysarthria	tremors	cramps	dystonia	visual	cognition	handwrit	sleep	migraine
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bladder	hemiatrop	ichthyosis	short neck	contractu	mmse	pale disc	retina	slow sacc
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n	n	n	n	n	n	n	n	y
n	n	n	n	n	n	n	n	n
n	n	vitiligo	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	y
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n	n	n	n	n	n	n	nn	n

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n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	y
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n	n	n	n	n	n	n	n	y
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n	n	n	n	n	n	n	n	n
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n	n	n	n	n	n	n	n	y
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	y
n	n	n	n	n	n	n	n	n
n	n	n	n		n	n	n	n
n	n	n	n	n	n	n		n
n	n	n	n	n	n	n	n	n
n	n	n	n	n		n		

pursuits	gaze rest	5th n	7th n	8th n	9/10th	12th n	wasting	weakness
y	n	n	n	n	n	n	n	n
y	n	n	n	n	n	n	n	n
y	y	y	y	n	y	y	y	y
y	y	y	y	n	n	y	y	y
y	y	y	y	n	y	y	y	y
n	n	n	n	n	n	n	n	n
y	y	y	y	n	y	y	y	y
y	n	y	y	n	y	y	y	n
y	n	y	n	n	y	y	n	n
y	n	y	n	y	y	y	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
y	n	n	n	n	n	y	y	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
y	n	y	n	n	y	y	n	n
y	n	y	n	n	n	n	n	n
y	n	y	n	n	n	n	n	n
n	n	n	y	n	n	n	n	n
y	n	y	n	n	n	n	n	n
y	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	y	n	n	n	n	n	n
y	n	n	n	n	n	y	n	n
y	y	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	y	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
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n	n	y	n	n	n	n	n	n
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y	n	y	n	n	n	n	n	n
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n	n	n	n	n	n	n	n	n
y	n	y	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	y	n	n	n	n	n	n
n	n	n	n	n	n	y	n	n

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n	n	n	n	n	n	y	n	n
n	nn	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
y	n	y	n	n	n	n	n	n
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y	n	y	n	n	n	n	n	n
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n	n	n	n	n	n	n	n	n
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pyramidal	per nerve	dystonia	chorea	myoclonus	gait ataxia	tremors	fascicula	extrapyr
y	n	n	n	n	y	y	n	n
y	n	n	n	n	y	y	n	n
y	y	y	n	n	y	y	n	n
y	y	n	n	n	y	n	n	n
y	y	y	n	n	y	y	y	n
n	n	y	n	n	n	n	n	n
y	y	y	n	n	y	y	n	y
y	n	n	n	n	y	n	n	n
y	n	n	n	n	y	n	n	n
y	y	n	n	n	y	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	y	y	n	n	n	n	y	n
n	n	n	n	n	n	n	nn	n
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n	n	n	n	n	n	n	n	n
n	n	y	n	n	y	n	n	n
n	y	n	n	n	y	n	n	n
n	n	n	n	n	y	y	n	n
n	n	n	n	n	y	n	n	n
n	n	n	n	n	y	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	n	n	n	n
n	n	n	n	n	y	n	y	n
n	y	n	n	n	y	n	n	n
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n	n	n	n	n	n	n	n	n
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n	y	n	n	n	n	n	n	n
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n	y	n	n	n	y	n	n	n
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n	n	n	n	n	y	n	n	n
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n	n	n	n	n	y	n	n	n
n	n	n	n	n	n	nn	n	n
y	n	n	n	n	n	n	n	n
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